FORMULATION AND EVALUATION OF MOUTH DISSOLVING LORATADINE TABLET - AS NOVEL APPROACH

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MASTER OF PHARMACY

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Submitted by

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(Accredited by NAAC, with CGPA of 2.74 on a four point scale at B-Grade)

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CERTIFICATE

This is to certify that the research work entitled **"FORMULATION AND EVALUATION OF MOUTH DISSOLVING LORATADINE TABLET - AS NOVEL APPROACH"** submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **J.SENTHIL** (Regd. No.26106009) in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2011 - 2012.

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DEDICATED

TO

MY BELOVED

PARENTS…

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS USED

%	Percentage
°C	Degree Celsius
µg	Microgram
λ max	Absorption maximum
BP	British Pharmacopoeia
CDR	Cumulative Drug Release
DE	Dissolution Efficiency
F	Formulation
FTIR	Fourier Transform Infra-Red
Gm	Gram
MDT	Mouth Dissolving Tablet
SSG	Sodium starch glycollate
CP	Crospovidone
CCS	Croscarmellose sodium
HCl	Hydrochloride
IP	Indian Pharmacopoeia
LOD	Loss on Drying
M	Molarity
M	Slope, Units of response
MCC	Microcrystalline cellulose
Mg	Miligram
Mp	Melting point
N	Normality

ODT	Orodispersible Tablet
pH	Negative Logarithum of hydrogen ion
Ppm	parts per million
RH	Relative Humidity
Rpm	Revolutions per minute
S.D.	Standard Deviation
T	Time
USP	United State Pharmacopoeia
UV-VIS	Ultraviolet-Visible

Introduction

1.INTRODUCTION

1.1. Mouth Dissolving Tablets *(Kuchekar B.S et al., 2003)*

Drug delivery via the oral mucosa is a promising route, when one wishes to achieve a rapid onset of action or improved bioavailability for drugs with high first-pass metabolism. Thus, there is a growing interest in developing alternative dosage forms, i.e. orally fast disintegrating tablets, which allow a rapidly dissolving drug to absorb directly into the systemic circulation through the oral mucosa. These kinds of dosage forms are also convenient for children, elderly patients with swallowing difficulties, and in the absence of potable liquids. However, in addition to formulation considerations, the properties of the active compound have to be appropriate in order to achieve drug delivery into systemic circulation after intra oral administration. The drug has to be soluble, fast dissolving and stable, and this might represent an obstacle for lipophilic drugs. Due to the small volume of saliva in the oral cavity, the therapeutic dose of an intra oral drug must be relatively small.

Among the different routes of administration, the oral route of administration continues to be the most preferred route due to various advantages including ease of ingestion, avoidance of pain, versatility and most importantly patient compliance. The different dosage forms include tablets and capsules. The important drawback of these dosage forms for pediatric and geriatric patients is being difficulty in swallowing. Nearly35% of the general population, especially the elderly patients and children suffer from dysphagia or difficulty in swallowing, which results in high incidence of

noncompliance and ineffective therapy. Swallowing problems also are very common inyoung individuals because of their poorly developed muscular and nervous systems. Other groups who may experience problems in swallowing conventional oral dosage forms are the patients with tremors of extremities, mentally ill, developmentally disabled, non co-operative patients and patients with reduced liquid intake plans or patients suffering from nausea. The swallowing problems are also common in some cases such as patients with motionsickness, sudden episodes of allergic attack or coughing and due to lack of water.

To overcome these problems, formulators have considerably dedicated their effort to develop a novel type of tablet dosage form for oral administration, i.e., one, which disintegrates and dissolves rapidly in saliva without the need for drinking water. The tablet is placed in the mouth, allowed to disperse or dissolve in the saliva. These tablets usually dissolve within 15 seconds to 2 minutes. The faster the drug goes into solution, the quicker the absorption and onset of clinical effect.

Less frequently, they are designed to be absorbed through the buccal and oesophageal mucosa as the saliva passes into the stomach. In the latter case, the bioavailability of a drug from rapidly disintegrating tablets may be even greater than that observed for other standard dosage forms.

The fast dissolving tablets also offer advantages over other oral dosage forms such as effervescent tablets, suspensions, chewing gum or chewing tablets, which are commonly used to enhance patient compliance.

The advantages of rapidly disintegrating tablets are being recognized in both industry and academia. Their growing importance was underlined recently when the European Pharmacopoeia adopted the term mouth dissolving tablet as a "tablet to be placed in the mouth where it disperses rapidly before swallowing.

1.1.1. Anatomic and Physiologic Features of the Oral Cavity *(Anne Waugh , 2006)*

The surface area of the oral mucosa is about 100 cm^2. Three different types of oral mucosa are recognized: the mucosa, the lining mucosa, and the specialized mucosa. The masticatory mucosa, representing 25% of the total oral mucosa, is100–200μm thick and covers the gingiva and the hard palate. It is tightly attached to underlying structures and subjected to abrasion and shear stress during mastication. The lining mucosa (60% of the total oral mucosa) is 500–800μm thick and covers the lips, cheeks, soft palate, lower surface of the tongue and the floor of the oral cavity. The specialized mucosa (15% of the total oral mucosa) is present on the dorsum of the tongue and is involved in taste.

1.1.1.1. Buccal Epithelium:

The buccal epithelium is a non-keratinized stratified squamous epithelium, composed of multiple layers of cells that show different patterns of maturation between the deepest cells and the surface. The basal cells of the buccal epithelium are capable of division and maintain a constant epithelial population as cells move toward the surface. Tissue homeostasis requires differentiation followed by migration and desquamation of the superficial cells. The prickle cells (intermediate layer) accumulate lipids and cytokeratins of low molecular weight that do not aggregate to form

filaments. An intracellular lipid portion is packaged in small organelles called membrane-coating granules or lamellar granules. Such granules migrate towards the apical surface of the cell, where their membrane fuses with the cell membrane and their lipid content is extruded in the extracellular space. The buccal epithelium lacks tight junctions, which are common to intestinal and nasal mucosa, but is endowed with gap junctions, glydesmosomes and hemidesmosomes, which are loose intercellular links. The epithelium rests on the basal membrane, an irregular saliva continuous interface between the epithelium and the connective tissue. The basal membrane anchors the epithelium to the connective tissue and improves the barrier function of the epithelium, preventing large molecules from passing through the oral mucosa.

Although buccal absorption is not the specific goal of oral fast- dissolving tablets, this can occur when the drug is released in the oral cavity in contact with buccal mucosa. The drug transport mechanism through the buccal mucosa involves two major routes:

- Transcellular (intracellular)
- Paracellular (intercellular)

The transcellular route involves passage through the cellular membranes with a polar and a lipid domain, while the paracellular route essentially consists of passive diffusion through the extracellular lipid domain. It is generally recognized that the lipid matrix of the extracellular space plays an important role in the barrier function of the paracellular pathway, especially with compounds that are hydrophilic and have a high molecular weight, such as peptides.

1.1.1.2. Vascularization of the Oral Mucosa

Arterial, venous and lymphatic capillaries penetrate the multi- layered epithelium, infiltrating the connective tissue. The oral mucosa is primarily supplied by the external carotid artery, which serves the large buccal blood vessels. The floor of the mouth, the root of the tongue and the cheek mucosa are the most highly vascularized areas. Vascular drainage from the oral mucosa is primarily via the lingual, facial and retromandibular veins, which flow together into the internal jugular vein. This is the mechanism responsible for by passing first-pass hepatic metabolism.

1.1.1.3. Salivary Flow

Saliva is the medium for disintegrate or dissolution for drug formulations designed to disintegrate/dissolve in the oral cavity; for this reason, the properties of saliva are crucial to oral fast-dissolving tablets. The saliva is primarily secreted in the oral cavity by parotid, submandibular (submaxillary) and sublingual glands, and also by numerous minor glands. The main constituent of saliva is water (99.5% w/v). The remaining 0.5% w/v consists of dissolved compounds; in fact, saliva is a hypotonic solution (150–200 mOsm) compared with extracellular fluids (300 mOsm). The principal components of saliva are: inorganic electrolytes (0.2% w/v), including sodium, potassium, calcium, magnesium, bicarbonate and phosphates; gases (carbon dioxide, nitrogen, oxygen); nitrogen products such as urea and ammonia; ascorbic acid (vitamin C); creatinine; and mucins (high-molecular-weight glydesmosomes coproteins, which render the saliva viscous and adhesive). Saliva also contains amino acids and proteins, digestive enzymes (salivary α-amylase [ptyalin], lipase, maltase,

and lysozyme with antibacterial activity), proteolytic enzymes (moderate levels of esterase, carbohydrases and phosphatases), serum albumin and immunoglobulins.

Saliva has a weak buffering capacity and its normal pH value is slightly acid (pH 6-7); however, salivary flow pH can range from 5.3 (low flow) to 7.8 (peak flow). The accepted range of normal salivary flow is approximately 0.1–0.2 ml/min, increasing to 7 ml/min upon stimulation. Saliva wets the entire oral cavity and the resulting mucus layer ranges from 1 to 400μm in thickness, forming a physical barrier to drug permeation and a useful substrate for mucoadhesive drug delivery systems.

1.1.2. The Ideal Characteristics of Mouth Dissolving Tablet *(Kuchekar B.S, 2003)*

- Requires no water for oral administration, yet dissolve or disintegrate in the mouth in a matter of seconds
- Allow high drug loading.
- Bitter taste to be masked.
- Have a pleasant mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Be portable without fragility concerns.
- Exhibit low sensitivity to environmental conditions such as humidity and temperature.
- Allows the manufacture of tablets using conventional processing and packaging equipment at low costs

1.1.3. Requriment of Mouth Dissolving Tablets an ideal MDT should

(Abhishek Gupta et al.,2010)

- Require no water for oral administration, yet dissolve /disperse/ disintegrate in mouth in a matter of seconds.
- Have small to moderate molecular weight.
- Good stability in water and saliva, to permeate oral mucosal tissue.
- Ability to diffuse and partition into the epithelium of the upper GIT (log P>1, or preferably>2).
- Have an acceptable taste masking property.
- Be harder and less friable.
- Be compatible with taste masking.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions as humidity and temperature.
- Allow the manufacture of tablet using conventional processing and packaging equipment at low cost

1.1.4. Advantages of MDDDS *(Abhishek Gupta et al.,2010)*

1. Ease of administration to patients who cannot swallow, such as the elderly, strokvictims and bedridden patients; patients who should not swallow, such as renalfailure patients; and who refuse to swallow, such as paediatrics, geriatric and psychiatric patients.

2. Patient's compliance for disabled bedridden patients and for travelling and busy people, who do not have ready access to water.
3. Good mouth feel property of MDDDS helps to change the basic view of medication as "bitter pill", particularly for paediatric patients due to improved taste of bitter drugs.
4. Convenience of administration and accurate dosing as compared to liquid Formulations.
5. Benefit of liquid medication in the form of solid preparation.
6. More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action.
7. Pregastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.

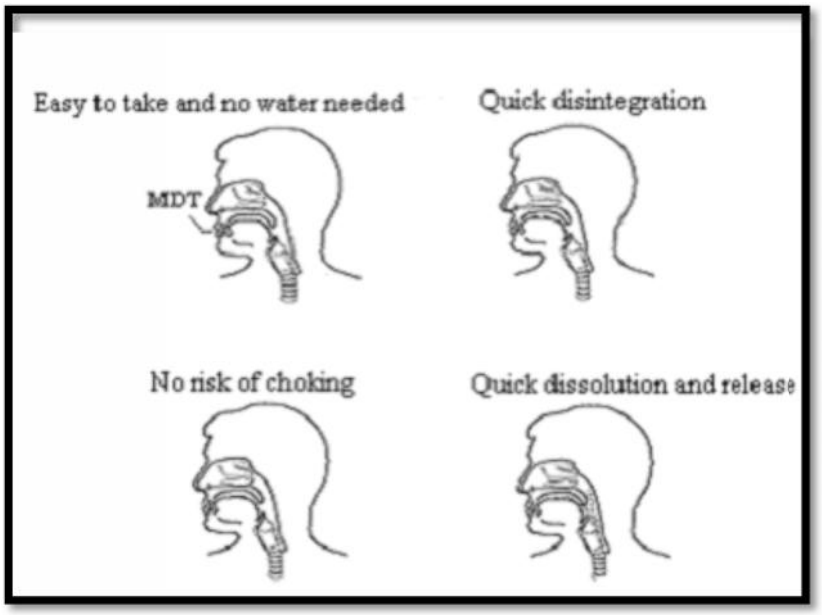


Figure 1.1: Diagram Showing Advantages of MDT

1.1.5. Disadvantages/Limitations of Mdts:

(Kuchekar B.S, 2003, Rangasamy Manivannan, 2009)

Certain drugs cannot be formulated as MDT's because of the following limitations:

- The major disadvantage of MDTs is its mechanical strength.
- Several MDTs are hygroscopic and cannot maintain physical integrity under normal condition from humidity which calls for specialized product packaging.
- MDTs are very porous and soft-moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle which are difficult to handle, often requiring specialized peel-off blister packaging.
- Bitter drugs or drugs with a disagreeable odour are difficult to formulate as MDTs. Special precautionary measures have to be taken before formulating such type of drugs.

1.1.6. Challenges To Develop Mdts: *(Suresh Bandari et al., 2010)*

- Achieve rapid disintegrate of tablet.
- Avoid increase in tablet size.
- Possess sufficient mechanical strength.
- Leave minimum or no residue in mouth.
- Protection from moisture.
- Good package design.
- Compatible with taste masking technology.
- Not affected by drug properties

1.1.7. Need of Fast Disintegrating Tablets:

The need for non-invasive delivery systems continues due to patients' poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

The current needs of the industry are improved solubility/stability, biological half-life and bioavailability enhancement of poorly absorbed drugs. Key issues facing the biopharma industry are to improve safety (decreasing gastrointestinal side effects), improve efficacy for organ targeting, and improved compliance via sustained release or easy to swallow.

Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical companies to survive.

Pharmaceutical marketing is another reason for the increase in available fast-dissolving/disintegrating products. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. In this regard, fast-dissolving/disintegrating tablet formulations are similar to many sustained release formulations that are now commonly available. An extension of market exclusivity, which can be provided by a fast-dissolving/disintegrating dosage form, leads to increased revenue, while also targeting underserved and under-treated patient populations. Although the cost to manufacture

these specialized dosage forms exceeds that of traditional tablets, this additional cost is not being passed on to the consumer.

Generally, the following points are considered for patient compliance in case of Epileptic patients,

- A rapid onset of action is necessary for immediate relief.
- Patient has difficulty to swallow tablet or any another dosage form when unconscious.
- Geriatrics has difficulty to swallow the dosage form.

Considering the above points, Patient convenience and compliance oriented research has resulted in bringing out safer and newer drug delivery systems. Recently Fast dissolving drug delivery systems have started gaining popularity and acceptance with increased consumer choice, for the reason of rapid disintegrate or dissolution, self administration even without water.

1.1.8. Salient Features of Mouth Dissolving Drug Delivery System (MDDDS)

- Ease of administration to pediatric, geriatric and psychiatric patients who refuse to swallow a tablet.
- Convenient for administration and accurate dosing as compared to liquids.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are depressed.
- Good mouth feel property of MDDDS helps to change the basic impression of medication as ‘Bitter Pill’ particularly for pediatric patients.

- As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.
- Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach, which enhances bioavailability of drugs by avoiding hepatic metabolism.
- Ability to provide advantage of liquid medication in the form of solid preparation.

1.2. Methodology Employed For Mouth Dissolving Formulations

(Abhishek Gupta et al.,2010)

1.2.1. Melt granulation

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate, PEG – 6 – stearate). Superpolystate is a waxy material with a melting point of 33–37°C and a HLB value of 9. So it will not only act as a binder and

increase the physical resistance of tablets but will also help the disintegrate of the tablets as it melts in the mouth and solublises rapidly leaving no residues.

1.2.2. Phase transition process

It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making FDTs without any special apparatus. FDT were produced by compressing powder containing erythritol (melting point: 122 °C) and xylitol (melting point: 93- 95 °C), and then heating at about 93 °C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol.

1.2.3. Sublimation

In this method a subliming material like camphor, is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva. Granules containing nimusulide, camphor, crospovidone, and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by vacuum exposure. Conventional methods like dry granulation, wet granulation and direct

compression with highly soluble excipients, super disintegrants and/or effervescent systems can also be used.

1.2.4. Three-dimensional Printing (3DP)

Three-dimensional printing (3DP) is a rapid prototyping (RP) technology. Prototyping involves constructing specific layers that uses powder processing and liquid binding materials. A novel fast dissolving drug delivery device (DDD) with loose powders in it was fabricated using the three dimensional printing (3DP) process. Based on computer-aided design models, the DDD containing the drug acetaminophen were prepared automatically by 3DP system. It was found that rapidly disintegrating oral tablets with proper hardness can be prepared using TAG. The rapid disintegrate of the TAG tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume.

1.2.5. Mass Extrusion

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste.

1.2.6. Spray drying

In this technique, gelatin can be used asa supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-

dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegrate and enhanced dissolution. Maximum drug release and minimum disintegrate time were observed with Kollidon CL excipient base as compared to tablets prepared by direct compression, showing the superiority of the spray dried excipient base technique over direct compression technique.

1.2.7. Cotton Candy Process

The FLASHDOSE® is a MDDDS manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of the medicament. The Shearform technology is employed in the preparation of a matrix known as 'floss', made from a combination of excipients, either alone or with drugs. The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F. However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose. This modification permits the safe incorporation of thermolabile drugs into the formulation. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouthfeel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps as detailed below.

1.2.7.1. Floss Blend

In this step, 80% sucrose in combination with mannitol/dextrose and 1% surfactant is blended to form the floss mix. The surfactant acts as a crystallization enhancer in maintaining the structural integrity of the floss fibers. It also helps in the conversion of amorphous sugar into crystalline form from an outer portion of amorphous sugar mass and subsequently converting the remaining portion of the mass to complete crystalline structure. This process helps to retain the dispersed drug in the matrix, thereby minimizing migration out of the mixture.

1.2.7.2. Floss Processing

The floss formation machine uses flash heat and flash flow processes to produce matrix from the carrier material. The machine is similar to that used in 'cotton-candy' formation which consists of a spinning head and heating elements. In the flash heat process, the heat induces an internal flow condition of the carrier material. This is followed by its exit through the spinning head (2000–3600 rpm) that flings the floss under centrifugal force and draws into long and thin floss fibers, which are usually amorphous in nature.

1.2.7.3. Floss Chopping and Conditioning

This step involves the conversion of fibers into smaller particles in a high shear mixer granulator. The conditioning is performed by partial crystallization through an ethanol treatment (1%) which is sprayed onto the floss and subsequently evaporated to impart improved flow and cohesive properties to the floss.

1.2.7.4. Blending and Compression

Finally, the chopped and conditioned floss fibers are blended with the drug alongwith other required excipients and compressed into tablets. In order to improve the mechanical strength of the tablets, a curing step is also carried out which involves the exposure of the dosage forms to elevated temperature and humidity conditions, (40 °C and 85% RH for 15 min). This is expected to cause crystallization of the floss material that results in binding and bridging to improve the structural strength of the dosage form.

1.2.8. Tablet Molding

Molding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30ºC under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin,

polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

1.2.9. Lyophilization or Freeze-Drying

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

1.2.10. Direct Compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT

because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

1.2.10.1. Superdisintegrants

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegrate and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegrate. For the success of fast dissolving tablet, the tablet having quick dissolving property which is achieved by using the super disintegrants, Some important examples of super disintegrants are given in **Table 1** with their mechanism of action.

1.2.10.2. Sugar Based Excipients

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

1.2.11. Nanonization

A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This

technique is especially advantageous for poor water soluble drugs. Other advantages of this technology include fast disintegrate/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

1.3. Superdisintegrants *(www.pharmainfo.net)*

A disintegrant helps the tablet to break up into smaller piecesupon contact with aqueous solution. Fast disintegrate ofa tablet matrix in the oral cavity facilitates swallowing andincreases the surface area of the tablet particles, which enhancesthe rate of absorption of the active ingredient to achieve the desired therapeutic effect. Every marketed tablet has a certainlevel of disintegrant and it is important to investigate whichand how much disintegrant is necessary for a given tabletformulation.Disintegrate starts when a small amount of water or salivacontacts the dosage form (wetting) and penetrates the tabletmatrix by capillary action. Therefore, the material properties ofpharmaceutical excipients and also the matrix structure includingpore size and distribution need to be considered for successfulformulation development. Since most disintegrants swell to someextent, swelling pressure is generally considered the main factorfor tablet disintegrate. Disintegrants or superdisintegrantswith efficient disintegrating properties at relatively low levels can be used in the formulation of MDTs. They are generally added ata level of 1–10% (w/w%).

Disintegrate efficiency is based on the force-equivalentconcept (the combined measurement of swelling forcedevelopment and amount of water absorption). Forceequivalence expresses the capability of a disintegrant totransform absorbed water into swelling (or disintegrating) force. The optimization of tablet disintegrate is commonlydone by mean of the disintegrate critical concentration.Below this concentration the tablet disintegrate time isinversely proportional to the disintegrant concentration.Above the critical concentration, the disintegrate timeremains approximately constant or even increased.One of the most desirable propertiesof disintegrants is rapid swelling without an accompanyingviscosity increase (no gel formation), because high viscosity onthe surface of the tablet will hinder water penetration into thetablet matrix to slow disintegrate.

There are a lot of disintegrants and superdisintegrants onthe market and most of them can be considered for use in MDTs.Typical examples includes crospovidone (crosslinked PVP),croscarmellose (crosslinked cellulose), sodium starch glycolate. (crosslinked starch), and low-substituted hydroxypropylcellulose. Crospovidone is a synthetic and water insolublecrosslinked homopolymer with the chemical structure of N-vinyl-2-pyrrolidone. A unique one-step polymerizationprocess known as ‘‘popcorn’’ polymerization is used to synthesize crospovidone polymers. Crosslinking chemically‘‘entangles’’ the polymer chains and is a major determinant of theproduct’s properties. This process results in a porous structurewith densely crosslinked polymers and a morphology thatrapidly wicks liquids into the particle to enhance swelling anddisintegrate. Crospovidone polymers are non-ionic so theirdisintegrate properties

are independent of pH changes in thegastrointestinal tract. Moreover, they do not form gels.

Disintegrants are usually waterinsoluble materials that swell on contact with moisture, thereforethe addition of excess disintegrant can lead to grittiness aftertablet disintegrate. The appropriate disintegrant and disintegrantquantity should be carefully investigated for a given MDT formulation.The particle size distribution of Kollidon CL and Polyplasdone XL is similar. However, bulk and tappeddensities of the both are significantly different due to thesmoother surface of Kollidon CL or the porous structure of Polyplasdone XL. Kollidons CL-F and CL-SF have lower bulkdensities than that of Polyplasdone XL because of their smallerparticle sizes. Promojel has the highest bulk and tapped densitiesand Ac-Di-Sol is in between Kollidon CL and Primojel. Selection of the right disintegrant depends on the formulationapplication and preparation procedure. For example, when MDTs are prepared using lactose as a diluent, *invivo* disintegratetime is dependent on the type of disintegrant.

Crospovidone can work as an efficient disintegrant with fast swelling properties. When mannitol and crospovidone were formulated by a direct compression method, the effects of the amount of mannitol and crospovidone as well as the compression force on the characteristics of the tablet were investigated. An optimum tablet formulation, containing 34% mannitol and 13% crospovidone, was recommended and provided a short wetting time of 17 s and a sufficient crushing strength of 40 N. MDTs were prepared by direct compression using microcrystalline cellulose (MCC) and low-substituted hydroxypropyl cellulose (L-HPC) as

disintegrants. It was found that the ratios of the two disintegrants MCC: L-HPC in the range of 8: 2 to 9: 1 showed the shortest disintegrate times.On the other hand, poly (acrylic acid) superporous hydrogel (SPH) microparticles were reported to be a super-disintegrant having a unique porous structure and they were added as a wicking agent to decrease disintegrate time.

1.3.1. Commonly used superdisintegrants: *(Suresh Bandari, 2010)*

Table 1.1: Commonly Employed Superdisintegrants in Mouth Dissolving Tablets

Superdisintegrant	Nature	Particle size	Mechanism
Crospovidone	Crosslinked homopolymer of N-vinyl-2-pyrrolidone	Particle size-100µm	Both swelling and wicking
Croscarmellose sodium	Cross-linked form of sodium CMC	Insoluble in water. Particle size 200 mesh	Swelling
Sodium starch Glycolate	Crosslinked low substituted carboxymethyl ether of poly-glucopyranose	Insoluble in water. Particle size 140 mesh	Water uptake followed by rapid and enormous swelling
Acrylic acid derivatives	Poly(acrylic acid) super porous hydrogel	Insoluble in organic solvents, disperses in cold water	Wicking action
Effervescent mixture	Citric acid,tartaric acid,sodium bicarbonate,sodium salt of alginic acid	Crystalline nature	Effervescence
Sodium alginate	Sodium salt of alginic acid	Slowly soluble in water, hygroscopic in nature	Swelling
NS-300	Carboxy methyl cellulose (CMC)	Particle size 106 µm	Wicking type
ECG-505	Calcium salt of CMC	Particle size 106µm	Swelling type
L-HPC	Low hydroxyl propyl cellulose	Particle size 106µm	Both swelling and wicking

1.4. Various mechanism of tablet disintegrate *(Abhishek Gupta et al.,2010)*

The tablet breaks into primary particles by one or more of the mechanisms listed below

- By capillary action
- By swelling
- Because of heat of wetting
- Due to disintegrating particle/particle repulsive forces
- Due to deformation
- Due to release of gases
- By enzymatic action

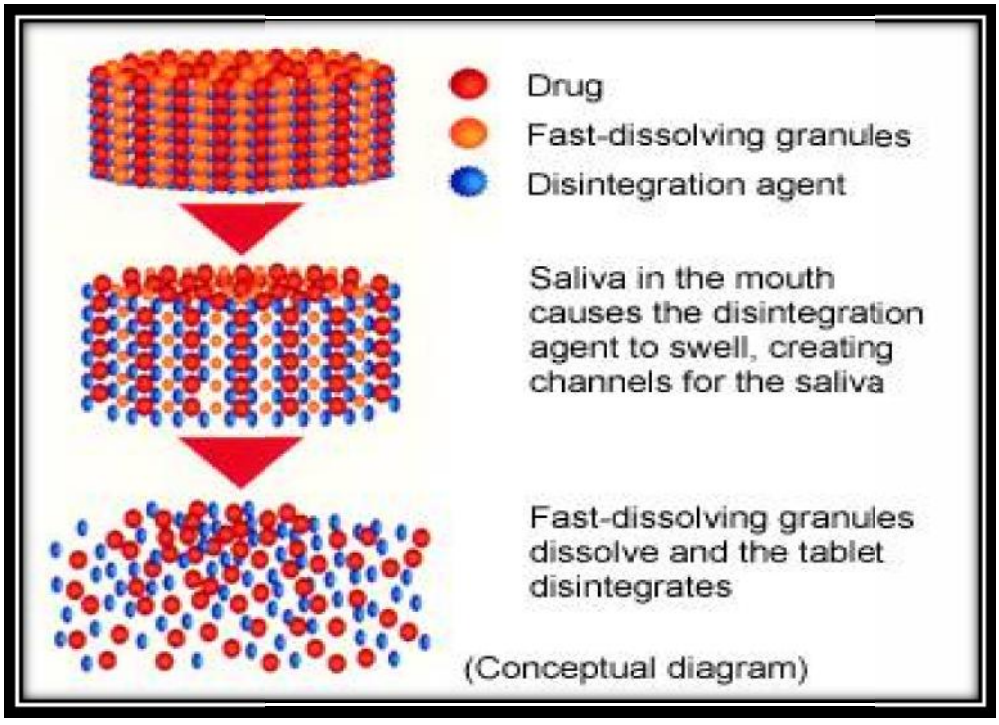


Figure 1.2: Conceptual design of tablet Disintegrate

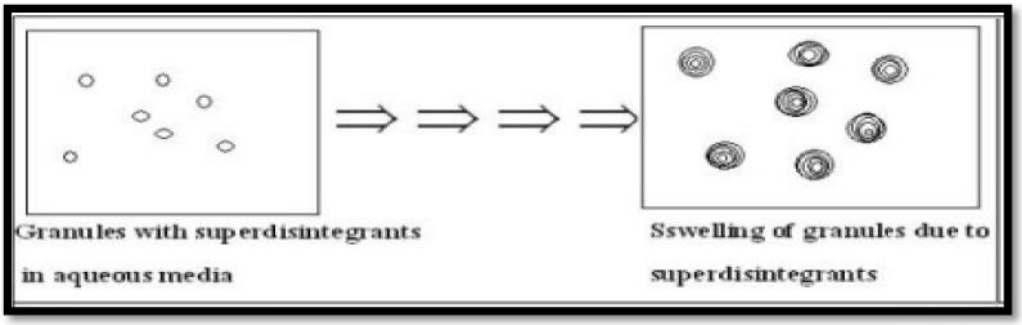


Figure 1.3: Mechanism of superdisintegrants by swelling

Ascending order of highest swelling capacity of superdisintegrants

CCS>CP>SSG *(Dhanyakumar D. C., 2010)*

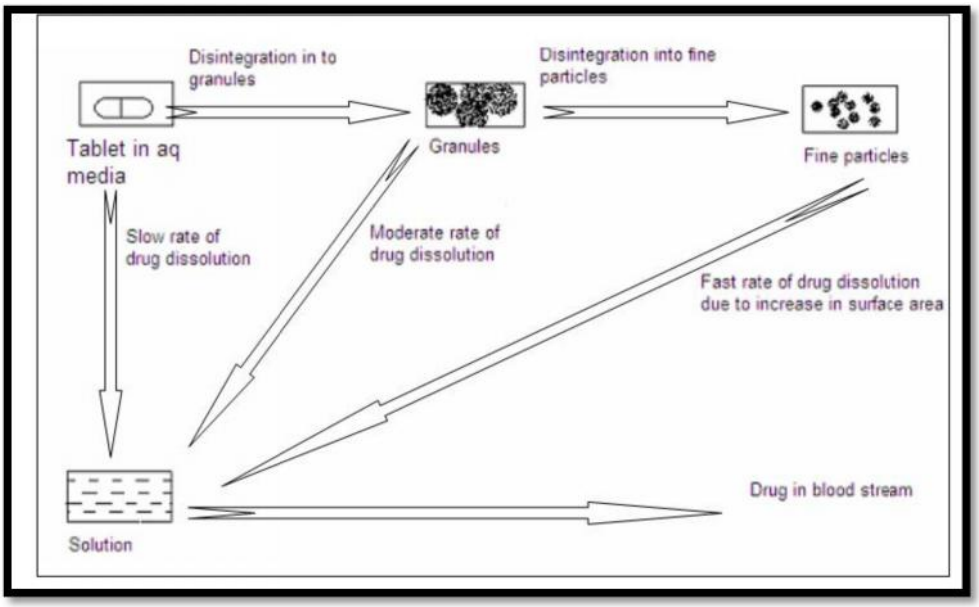


Figure 1.4: Mechanism of tablet disintegrate

1.4.1. By capillary action

Disintegrate by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles.

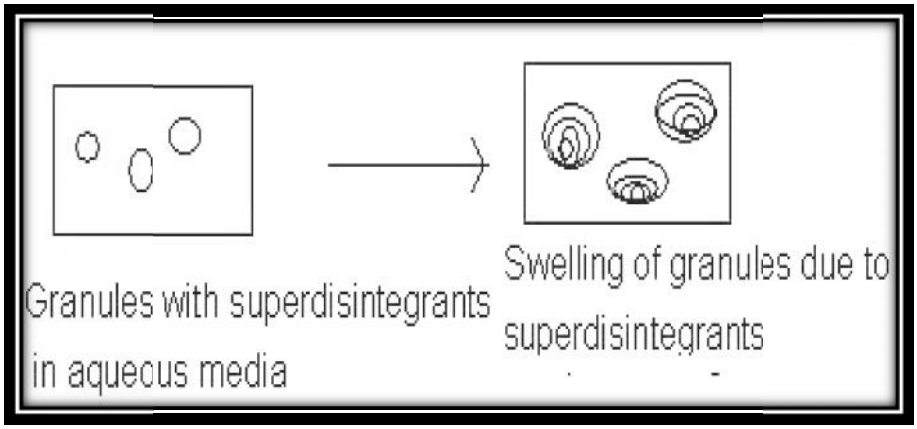


Figure 1.5: Disintegrate due to capillary action

1.4.2. By swelling:

Perhaps the most widely accepted general mechanism of action for tablet disintegrate is swelling Tablets with high porosity show poor disintegrate due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegrate is again slows down.

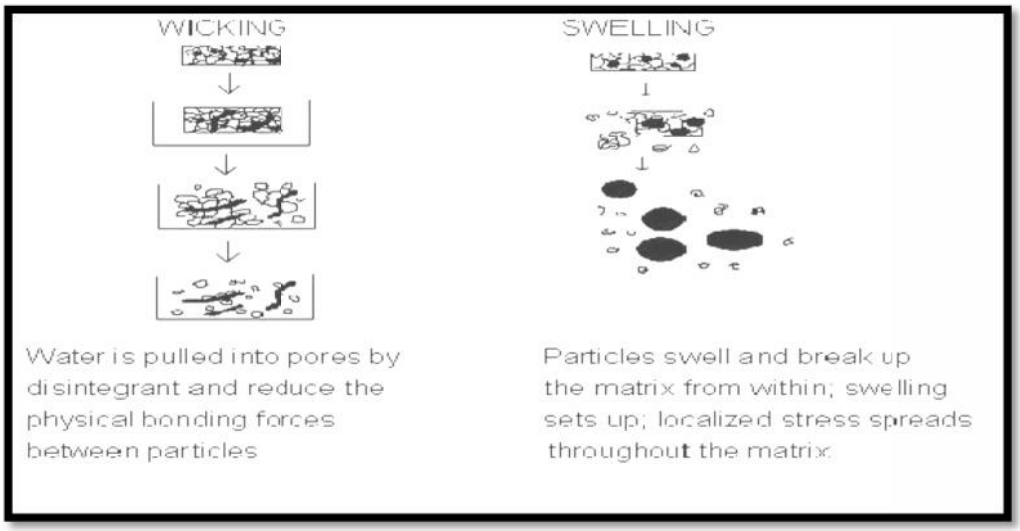


Figure 1.6: Disintegrate due to swelling and wicking

1.4.3. Because of heat of wetting (air expansion)

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegrate of tablet.

1.4.4. Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegrate attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non swelling particles also cause disintegrate of tablets.

1.4.5. Due to deformation and repulsion

Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet.

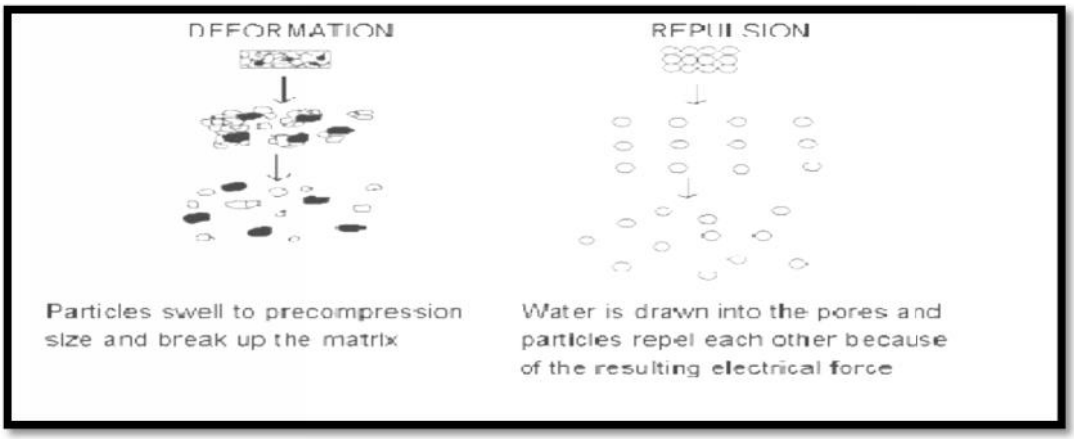


Figure 1.7: Disintegrate by deformation and repulsion

1.4.6. Due to release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

1.4.7. By enzymatic reaction

Table 1.2: Disintegrating Enzymes

Enzymes	Binder
Amylase	Starch
Protease	Gelatin
Cellulase	Cellulose and it's derivatives
Invertase	Sucrose

Here, enzymes presents in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegrate.

1.5. Strategies of Taste Masking: *(Roop K.Khar, 2001)*

Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with certain drugs. Four fundamental sensations of taste have been described:

- Sweet and salty, mainly at the tip.
- Sour, at the sides.
- Bitter, at the back.

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. Various techniques available for masking bitter taste of drugs include taste masking with ingredients such as flavors, sweeteners, and amino acids; taste masking by polymer coating; taste masking by conventional granulation; taste masking with ion-exchange resins; taste masking by spray congealing with lipids; taste masking by formation of inclusion complexes with cyclodextrins; taste masking by the freeze-drying process; taste masking by making multiple emulsions; and taste masking with gelatin, gelatinized starch, liposomes, lecithins or lecithin-like substances, surfactants, salts, or polymeric membranes.

1.5.1. Taste Masking with Flavors, Sweeteners, and Amino Acids

This technique is the foremost and the simplest approach for taste masking, especially in the case of pediatric formulations, chewable tablets, and liquid formulations. But this approach is not very successful for highly bitter and highly water soluble drugs. Artificial sweeteners and flavors are generally being used along with other taste-masking techniques to improve the efficiency of these techniques. Aspartame is used as a prominent sweetener in providing bitterness reduction. A very small concentration (0.8%) is effective in reducing the bitterness of 25% acetaminophen. Starch, lactose, and mannitol have also exhibited taste-masking

properties of caffeine. Anticholesterolemic saponin-containing foods, beverages, and pharmaceuticals are supplemented with amino acids (such as glycine and alanine) and flavors for bitterness control.

1.5.2. Taste Masking with Lipophilic Vehicles

- **Lipids:**

Oils, surfactants, polyalcohols, and lipids effectively increase the viscosity in the mouth and coat the taste buds, and therefore they are potential taste masking agents. Guaifenesin has improved taste when mixed with carnauba wax and magnesium aluminium silicate and then melt-granulated.

- **Lecithin and Lecithin-like Substances:**

Formulations with a large excess of lecithin or lecithin-like substances are claimed to control bitter taste in pharmaceuticals. Magnesium aluminum silicate with soybean lecithin is used to mask the unpleasant taste of talampicillin Hydrochloride. The drug is dissolved in or dispersed into an organic solvent such as chloroform. Lecithin is added to the solution or dispersion of the drug with stirring to give a blend. The blend is mixed with powdery excipients (e.g., magnesium aluminate metasilicate, synthetic aluminum silicate, lactose, mannitol, etc.), dried and granulated to give a taste-masked composition.

1.5.3.Taste Masking by Coating with Hydrophilic Vehicles

This is the simplest and most feasible option to achieve taste masking. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Coating of chewable tablets provides excellent taste

masking while still providing acceptable bioavailability. A specialized technique, i.e., micro emulsion technology, has been used for taste masking of powders, chewable tablets, and liquid suspensions.

1.5.4. Carbohydrates (Cellulose)

The taste of orally administered drugs can be masked by coating the drug with carbohydrates. Bitter solid drugs such as pinaverium bromide, a spasmolytic, has no bitter taste when formulated in an organoleptically acceptable manner by polymer coating with a mixture of cellulose or shellac and a second film forming polymer soluble at pH less than 5.

1.5.5. Taste Masking by Inclusion Complexation

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent, i.e., the host molecule, forming a stable complex. The complexing agent is capable of masking the bitter taste of drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds, thereby reducing the perception of bitter taste. This method is most suitable only for low dose drugs. Vander Waals forces are mainly involved in inclusion complexes. The suppression of bitter taste by cyclodextrin was in increasing order of alpha, gamma, and beta cyclodextrin. β-cyclodextrin is the most widely used complexing agent for inclusion type complexes. It is a sweet, nontoxic, cyclic oligosaccharide obtained from starch.

1.5.6. Solid Dispersion System

Solid dispersion have been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion) solvent or melting solvent method. Solid dispersion is also called as co precipitates for those preparation obtained by solvent method. Solid dispersion of drug with the help of polymers, sugar, or other suitable agents, is very useful for taste masking. The bitter taste of dimenhydrinate can be masked by preparing the solid dispersion of the drug with polyvinyl acetate phthalate. Solid dispersions using insoluble matrices or bland matrices may be used to mask the bitter taste of drugs. Also using them as absorbents on various carriers may increase the stability of certain drugs.

1.5.7. Prodrugs

A prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent drug. The alkyloxyalkyl carbonates of the clarithromycin 2' position have remarkably alleviated bitterness and improved bioavailability when administered orally.Tasteless/bitter le ss prodrugs of opioid analgesics and antagonists were formulated for improved buccal delivery. Tasteless prodrugs of nalbuphine Hydrochloride, naltrexone, naloxone, oxymorphone Hydrochloride, butorphanonol, and levallorphan were synthesized for buccal administration to improve bioavailability relative to that of oral dosing without the characteristic bitter taste.

1.5.8. Ion Exchange Resin

Another popular approach in the development of taste masking is based on ion exchange resin. Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. The resulting ion exchange is reversible and stiochiometric with the displacement of one ionic species by another.

Ion exchange resins can be classified into four major groups

- Strong acid cation-exchange resin.
- Weak acid cation-exchange resin.
- Strong base anion-exchange resin.
- Weak base anion-exchange resin.

Strong acid cation resins (sulfonated styrene di vinyl bezene copolymer product) function throughout the entire pH range and can be used for masking the taste of basic drugs. Weak acid cation exchange resins function at pH values above 6.0. Similarly, strong base anion-exchange resins function throughout the entire pH range and can be used for masking the taste of acidic drugs, while the weak base anion exchange resins function well below pH 7.0 Synthetic ion exchange resin have been used in pharmacy and medicine for taste masking or controlled release of drug as early as 1950.

1.5.9. Miscellaneous Taste-Masking Approaches

1.5.9.1. By Effervescent Agent

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have also been employed for use as taste-masking agents for dosage forms that are not dissolved in water prior to administration. A chewing gum composition of bitter medicament(s) was formulated to supply the medicament(s) to the oral cavity for local application or for buccal absorption. It comprises a chewing gum base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitizing composition (e.g., oral anesthetics such as benzocaine and spilanthol) and other nonactive materials, such as sweeteners, flavoring components, and fillers. Recently, effervescent tablets of fentanyl and prochlorperazine were developed to supply these drugs to the oral cavity for buccal, sublingual, and gingival absorption.

1.5.9.2. Salt Preparation

Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water-soluble ibuprofen salts in aqueous solution. The bitter taste of caffeine may be masked by formulating it as a carbonated oral solid preparation using sodium bicarbonate, ascorbic acid, citric acid, and tartaric acid. Magnesium aspirin tablets are rendered tasteless by preparing magnesium salts of aspirin. Penicillin prepared as N, N'-dibenzylethylene-diamine diacetate salts or N, N'-bis (deyhdroabiety) ethylenediamine salts is tasteless. Bitterness-reduced antitussive and expectorant compositions (tablets) of dihydrocodeine phosphate, DL-methylephedrine

Hydrochloride, and D-chlorpheniramine maleate contain magnesium salts, sweeteners, starch, and cellulose.

1.5.9.3. Freeze Drying Process

This method is used to develop fast-dissolving oral technologies such as Zydis and Lyoc technology. Zydis is a tablet-shaped dosage form that spontaneously disintegrates in the mouth in seconds. This is due to the high porosity produced by the freeze drying process. The Zydis process requires the active ingredient to be dissolved or suspended in an aqueous solution of water soluble structure formers. The resultant mixture is then poured into the preformed blister pockets of a laminate film and freeze dried. The two most commonly used structural excipients are gelatin and mannitol, although other suitable excipients can be used (e.g., starches, gums, etc.). This process is ideally suited to low solubility drugs as these are more readily freeze dried. Taste is very important for this type of dosage form and it is possible to produce palatable formulations by using artificial sweeteners (e.g., aspartame) and conventional flavors. Various drugs have been taste-masked by Zydis technology. These are lorazepam (Wyeth), piroxicam (Pfizer), loperamide (Janssen), ondansetron (Glaxo Wellcome), rizatriptan (Merck), loratadine (Schering Plough), olanzapine (Eli Lilly), selegiline (Elan), scopolamine/ chlorpheniramine (Taisho), etc.

1.6. Taste Assessment

Taste assessment one of the important quality control parameters for evaluation of taste masked formulation .Drug or formulation can be assessed using in vivo and in vitro method of taste evaluation parameters.

1.6.1. In vitro approaches taste assessment

1.6.1.1. In vitro drug release studies

Pharmacopoeial release studies have been modified by altering the chemical composition of the dissolution media (e.g. artificial saliva) and reducing the size of the basket screen size (screen size< 0.381 mm square opening) to prevent particles forms escaping. Taste masking is achieved when, in the early time points from 0-5 minutes the drugs substances in the dissolution medium is either not detected or amount is below the threshold for identifying its taste. Drug can be analyzed either spectrophotometrically or using HPLC. Of these HPLC is generally preferred especially when testing is performed in the presences of UV-absorbing component, such as flavorings and sweetener. A novel *invivo* buckle dissolution testing apparatus and method for the assessment of taste masking in oral dosages forms have recently been invented. The apparatus consists of a single, stirred, flow-through filtration cell including a dip tube designed to remove fine solid particles. Simulated saliva is used as the dissolution medium. The filtrated solution is removed from the apparatus continuously and used to analyze the dissolve drug.

1.6.1.2. Voltramettric electronic tongue

The Voltramettric electronic tongue developed by s-*sense consistent of four working metal electrode made of gold, platinum, iridium and rhodium an Ag/AgCl references and a stainless steel counter electrode. A relay box enables the working electrode to be connected consecutively, to form four standards three-electrode configurations. The potentially pulse are applied by a potentiostat which is controlled

by a personnel computer. The PC used to set and control the pulse, measure and store current response, and to operate the relay box.

1.6.1.3. Electronic tongue

The electronic tongue initially developed by the University of Taxes consists of light sources, a sensors array and detector. The light sources shines onto chemically adapted polymer beads arranged on a small silicon wafer, which is known as a sensors chip the beads change is color on the basis of the presences and quality of specific chemical. The change is color is capture by a digital camera and the resulting signal converted into data using video capture board and a computer.

1.6.2. In vivo approaches for taste assessment

In vivo studies, stimuli are applied on to the tongue of either human or animals.

1.6.2.1. Human taste panel studies

Human taste panel studies evaluated tastant (food, chemical, drug and so on) by estimating the gustatory sensation response in healthy human volunteers within well-controlled process. Such studies are there for also known as physiological evaluation, gustatory sensation testes or taste trials. They are sensitively measured of taste and are spastically designed to minimize bias and response within and between human volunteers. Well-established methodology for performing sensory analysis can be broadly divided into five types, namely discrimination taste. Scaling taste, experts testers, affective taste and descriptive methods and have been excellency discussed. Volunteers asses the taste quality and intensity of standard are taste stimuli on

different adjective scales including various properties of the sample, such as overall intensity, sweet, odor, bitter, metallic, cooling, hot, spicy, anesthetic, astringent etc. Each adjective can be rated as intensity rated on the scale zero to four a perhaps even up to nine points on the provided score rates.

1.6.2.2. Animal preference testes

Bottle performance and condition taste aversion taste are used for taste for determining taste preference and concentration-response properties of tastant by animal 3 and 4 rats, mice, cats and dogs can be used for the potentiometrically e-tongue, incorporating and array of artificial lipid-polymer membranes as a fingerprint devices, has been developed as a promising tool for use in the quality control of phytomedicines. The miniaturization of taste sensors is particularly interest for the food and pharmaceutical industries. A portable low-cost sensing system has been made that interfaces to a Voltramettric electronic tongue sensors. Screen-printing technologies have been used to develop disposable taste sensors.

1.7. Patented Technology for Mouth Dissolving Tablets

(*Bandari Suresh, 2008 ; Brahmeshwar Mishra, 2009)*

1.7.1. Zydus Technology

Zydus formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When Zydus units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not required water to aid swallowing. The Zydus matrix is composing of many materials designing to achieve a number of objectives. To impart

strength and resilience during handling, polymer such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which impart strength.

To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegrate while various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of Zydus units during freeze drying process or long term storage. Zydus products are packed in blister packs to protect formulation from moisture in the environment.

1.7.2. Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of drug, filler and lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring lowamount of active ingredients.

1.7.3. Orasolv Technology

CIMA labs have developed orasolv Technology. In this system active medicament is taste masked. It also contain effervescent disintegrating agent. Tablets are made by direct compression technique atlow compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable.

1.7.4. Flash Dose Technology

Flash dose technology has been patented by Ethypharm France**.** Nurofen meltlet, a new form of Ibuprofen as melt in mouth tablets prepared using flashdose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self- binding shear form matrix termed as "Floss Shear" form matrices are prepared by flash heat processing. This technology is also called as Cotton Candy Process.

1.7.5. Wowtab Technology

Wowtab technology is patented by Yamanouchi Pharmaceutical Co.WOW means "Without Water". In this process, combination of low mould ability saccharides and high mould ability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mould ability saccharide and granulated with a high mould ability saccharide and compressed into tablet.

1.7.6. Flashtab Technology

Prographarm laboratory have patented the flashtab technology. Tablet prepared by this system consist of active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation an dextrusion - spheronisation. All the processing utilized conventional tabletting technology.

1.8. The Following Category of Drugs Can be Formulated As Fast Dissolving Dosage Forms. *(www.pharmainfo.net)*

There are no particular limitations as long as it is a substance which is used as a pharmaceutical active ingredient.

Anti-epileptics, Analgesics, Anthelmintics, Anti-Arrhythmic agents, Anti-bacterial agents, Anti-coagulants, Anti-depressants, Anti-diabetics, Anti-gout, Anti-hypertensive Agents, Anti-malarial agents, Anti-migraine agents, Anti-muscarinic agents, Anti-neoplastic agents, Immunosuppressants, Anti-protazoal agents, Anti-thyroid agents, β-blockers, Cardiac inotropic agents, Corticosteroids, Diuretics, Anti-parkinsonian agents, Gastro intestinal agents, H1-receptor antagonists, Lipid regulating agent, Neuro -muscular agents, Nitrates and other anti-anginal agents, Nutritional agents, Opioid analgesics and Sex hormone.

1.8.1. Patient Counseling In Effective Use of Fast Dissolving Tablets

ODT developed offers significant advantages for various groups of patients, but the majority of patients receiving ODT have little understanding of this novel dosage form. Patients receiving ODT may be surprised when tablets begin to disintegrate/dissolve in mouth. As pharmacists are ideal persons to know about the recent technologies, thus have opportunity to educate the patient for effective treatment. Counseling of patients about this dosage form can avoid any confusion and misunderstanding in taking ODT. Patient information that needs to be provided includes

Storage of this dosage form as some of ODT developed may not have sufficient mechanical strength, which needs to be handled carefully.

Patients with Siogren's syndrome or dryness of mouth or who take anti cholinergic drugs may not be suitable candidates for administering ODT. Although no water is required to allow drug to disperse quickly and efficiently but decreased volume of saliva may slow the rate of disintegrate/dissolution and may reduce the bioavailability of the product

Patients need to be clearly told about the difference between effervescent and ODT. Some of technologies use effervescence, which experience a pleasing tingling effect on the tongue.

Although chewable tablets are available in market and patient need to be counseled about differences between chewable and ODT tablets. This ODT can be used easily in children who have lost their primary teeth and in geriatric patients who have lost their teeth permanently.

Patients may mistake fast-dissolving/disintegrating for effervescent tablets. Pharmacists may wish to stress the difference between the use of quick-dissolving and effervescent tablets. The Cima technologies, OraSolv and DuraSolv, use slight effervescence. Patients may experience a pleasant tingling on the tongue with OraSolv and DuraSolv.

With the pharmacists counseling, intervention and assistance about ODT, all patients receiving this novel dosage form could be more properly and effectively treated with greater convenience.

Table 1.3: List of Commercially Available MDTs *(www.pharmpedia.com)*

Trade Name	Active Drug	Manufacturer
Feldene Fast, Melt	Piroxicam	Pfizer Inbc., NY,USA
Claritin Redi Tab	Loratidine	Schering PloughCorp.,Kenilworth, USA
Mazalit MTL	Rizatriptan	Merckasnd Co., NJ, USA
Zyprexia	Olanzapine	Eli Lilly, Induanapolis, USA
Zofran ODT	Ondansetron	Glaxo wellcome, Middleselx, UK
Zoming – ZMT	Zolmitriptan	AstraZeneca, Wilmington, USA
Zeplar TM	Selegilline	Amarin Corp., London, UK
Tempra Quiclets	Acetaminophen	Bristol Myers Squibb, NY ,USA
Febrectol	Paracetamol	Prographarm. Chateauneuf, France
Nimulid MDT	Nimesulide	Panacea Biotech, New-Delhi, India
Torrox MT	Rofecoxib	Torrent Pharamceuticals, Ahmedabad
Olanex Istab	Olanzapine	Ranbaxy Labs Ltd., New-Delhi, India
Romilast	Montelukast	Ranbaxy Labs Ltd., New-Delhi, India
Relivia Flash dose	Tramadol HCl	Fuisz Technology, Ltd, India

Aim

And

Objective

2. AIM AND OBJECTIVE

AIM

Aim of present study is to formulate Loratadine mouth dissolving tablets by using different super disintegrants and evaluating its characteristics.

OBJECTIVE

The objective of present study is

1.The investigation was undertaken with a view to develop fast dissolving tablets to get the quick onset of action in treatment of a suddenly arising allergic reactions.

2. To evaluate the effect of three different superdisintegrants on disintegrate parameter and the wetting properties of the tablets.

3.For to inhibit and numb the test of Loratadine by using sensory approach method.

4. To avoid first pass metabolism by giving absorption of Loratadine from oral cavity, pharynx and oesophagus regions.

5. To develop mouth dissolving drug delivery system by simple and cost effective technique.

This mouth dissolving tablet of Loratadine will disintegrate rapidly in the patient mouth without need of water or chewing and released its drug content instantaneously with rapid disintegrate/dissolution, quick absorption from oral cavity, pharynx and esophagus in turn shows immediate relief. So this dosage form is more comfortable for paediatric, geriatric patients.

Thus, mouth dissolving tablets of Loratadine truly serve as Orodispersible Drug Delivery System because of its convenient nature.

Plan of work

3. PLAN OF WORK

The study was planned to carry out as follows,

1 Literature review

2 Selection of drug and excipients

3. Procurement of drug, Polymer and other excipients

4. Experimental work

A Preformulation study

- **Identification of drug**
  - By FTIR spectroscopy
  - By Melting point
- **Physicochemical parameter**
  - Organoleptic properties
  - Solubility profile
  - Loss on drying
- **Analytical methods**
  - Determination of absorption maxima.
  - Development of standard curve of Loratadine
  - Determination of % purity of drug
- **Determination of drug polimer compatibility**
  - By FTIR spectroscopy
  - By DSC thermal analysis

5. Formultion and characterization of powder blend

- Sodium starch glycollate (Explotab)
- Croscarmellose Sodium (Ac-Di-sol)
- Crospovidone (polyplasdone)

6. Evaluation of powder mixed blend of drug and excipients

- Angle of Repose
- Bulk Density
- Tapped Density
- Compressibility index
- Hausner ratio

7. Formulation and Compression of Mouth Dissolving tablet by direct compression method

8. Evaluation of compressed MD tablets

- Appearance
- Weight variation
- Thickness
- Hardness
- Friability
- Estimation of drug content
- Disintegration time
- Wetting time

- Water absorption ratio
- In-vitro Dissolution studies

9. Stability testing of optimized batch

10. Results and Discussion

11. Summary and Conclusion

12. Future Prospects

13. Bibliography

Literature Review

4. LITERATURE REVIEW

Abu Izza et al ., (2004). The method comprises of combining on active ingredient with a fast dissolving granulation. The fast dissolving granulation contains a low melting point compound that melts or softens at or below 37ºC and a water soluble excepient.

Ahmad I.S., Nafadi M.M., Fatahalla F.A. et al., (2006) Went ahead and formulated fast dissolving ketoprofen tablets using freeze drying technique in blister).

Chaudhari P.D. *et al.*,(2005) Carried out formulation and evaluation offast dissolving tablets of Famotidine by using different superdisintegrates (Ac-di-sol and Polyplasdone) with varyingconcentrations (2%, 3%, 4% and 5%) The bitter taste of Famotidinewas masked using Drug .Eudragit E-l00 in different ratios (1:1 –1:10). The dissolution release rate was found to be 100% in 4minutes.

Cirri M. and Mura P. Developed fast dissolving tablets of glyburide based on ternary solid dispersion with poly ethylene 6000 and surfactant . Glyburide a commonly used anti diabetic and oral hypo Glycemic agent shows very low aqueous solubility .Dissolution can represent major rate limiting step to oral absorption and consequently bio availability of scarcely water soluble, poorly wettable but highly permeable drugs. These drug are classified as class II compounds according to Biopharmaceutical classification (BCS) system. A simple technicque used to enhance the dissolution properties of poorly water soluble drugs is the addition of appropriate surfactant to the formulation. Their findings indicator that simultaneous presence of surfactant and a hydrophilic polymer gave rise to synergistic effect of their solubility and wetting properties towards the drug. On the same lines Liu C. and Desai K.G

made fast dissolving tablets based on enhancement of dissolution rate of valdecoxib using solid dispersion with poly ethylene glycol 4000.

Devi V.K. *et al.*,(2006) Carried out formulation of Orodispersible tablets of fluconazole using two different volatilizable compounds Viz. ammonium chloride and camphor by Wet Direct Compression method. Best formulations were chosen and compared with marketed conventional tablets. No significant difference between the technological properties of the prepared formulations and the marketed tablets.

Ganesh kumar Gudas , Manasa B, et al., (2010) Formulation and evalution of fast dissolving tablets of Chlorpromazine HCl an attempt has been made to prepare fast dissolving tablets of Cholorpromazine HCl in the oral cavity with enhanced dissolution rate. The tablets was prepared with five superdisintegrants. Eg Sodium starch glycolate ,Crospovidone , Croscarmellose , l-hac, pregelatinised starch. It was concluded that the fast dissolving tablets with proper hardness, rapidly disintegrating with enhanced dissolution can be made using selected superdisintegrants.

Gattani S.G. *et al.*, (2009) This study was aimed at development of Ondansetron Hydrochloride mouth dissolving tablets which can disintegrate or dissolve rapidly once placed in the oral cavity. This tablet is to combat emesis and nausea.

Hiremath J.G.,*et al.*,(2004) This article discusses the past and recent approaches and methodology for bitterness reduction for oral pharmaceuticals. Several Pharmaceuticals, active agents, numerous food and beverage products and bulking agents, have unpleasant bitter tasting components. In some cases, the bitter taste is an undesirable trait of the product or formulations and can considerably affect its acceptability by consumers. Bitter characteristics found in such system have been

eliminated or minimized by various known processes, but no universally applicable technology for bitterness inhibition has been recognized.

Keny R.V., et al., (2010) Mouth disintegrating tablets of rizatriptan benzoate were prepared using superdisintegrants Crospovidone, carboxymethylcellulose calcium, indion 414 and indion 234 using the direct compression method. The tablets disintegrsted *in vitro* and *in vivo* within 4 to 7 s and 6 to 19 s, respectively. Almost 90% of drug was released from all formulation within 20 min. The drug release from the formulations followed first order kinetics. The formulation containing combination of crospovidone and indion 234 was found to give the best results.

Abdel Bary A ,Omneya M., et al (2010) Fast dissolving tablets (FDTs) of amlodipine besylate were prepared by direct-compresion method. Nine formulae having three subliming agents at three different concentration levels were prepared to assess the most efficiency and critical concentration level. Twelve formulae having three subliming agents at the predetermined level and two superdisintegrants and their critical concentration level and coprocessed superdisintegrants and its critical concentration level.

Kuchekar B. S., *et al,*. (2003) Recent advances in Novel Drug Delivery System (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and achieve better compliance. One such approach is fast mouth dissolving tablet. Present review article focuses on significance of mouth dissolving dosage forms and the techniques and technologies available for their manufacturing.

Kuchekar B.S. *et al.*,(2004) Carried out formulation of mouth dissolving tablets of Sumatriptan succinate using super disintegrants like Sodium starch glycollate,

Carboxy methylcellulose sodium and Treated agar by Direct compression method. Almost 90% of drugs were released from all formulations within 10 minutes. The formulation containing combination of sodium starch glycollate and Carboxy methyl cellulose was found to give the best results.

Kuchekar B. S., *et al.,* (2006) Orodissolving tablets of Promethazine hydrochloride were prepared using superdisintegrants, sodium starch glycolate and cross carmellose sodium by direct compression method. The prepared tablets were evaluated for uniformity of weight, tensile strength, content uniformity, hardness, friability, wetting time, in vitro and in vivo dispersion time and in vitro drug release.

Lalla J.K. *et al.*,(2004) Studied the inclusion complex of Rofecoxib with Beta-cyclodextrin using ball milling technique has been prepared and evaluated. The tablet shows complete release of Rofecoxib in 12 minutes as compared to 20% drug release from conventional released marked tablets.

Luca Dobetti, *et al.,* (2001) The demand for fast-melting tablets (FMTs) has been growing during the last decade, particularly for children and the elderly who have difficulty swallowing tablets and capsules. These dosage forms are placed are placed in the mouth, allowed to disperse or dissolve in the saliva, and then swallowed without the need for water. The advantage of this convenient administration has encouraged both academia and industry to generate new fast-disintegrating formulations and technological approaches in this field. This article reviews the latest progress in the development of FMTs.

Mallikarjuna Setty C.*etal.*, (2008) In this literature MD tablet was prepared by direct compression method. Effect of superdisintegrants such as cross carmellose sodium, sodium starch glycollate, and crospovidone on wetting time, disintegrate time, drug content, in-vitro release and stability parameters has been studied. It is concluded that fast dispersible Aceclofenac tablets could be prepared by direct compression using superdisintegrants.

MishraD.N. *et al.*, (2005) Carried out formulation of rapidly disintegrating tablets of Valdecoxib using super disintegrants like sodium starch glycollate, Ac-di-sol, Crospovidone. The poor aqueous solubility of the drug results in variable dissolution rate hence poor bioavailability. In the present study, an attempt had been made to prepare fast disintegrating tablets of the drug using various superdisintegrants following direct compression technique. It was concluded that the fast dissolving tablets of the poorly soluble drugs can be made by direct compression technique using selective superdisintegrants showing enhanced dissolution i.e. improved bioavailability and hence better patient compliance and effective therapy.

Mishra D.N. *et al.*,(2006) Carried out formulation of rapidly disintegrating tablets of Meloxicam using super disintegrants like sodium starch glycollate, Ac-di-sol and low molecular weight HPMC. The disintegrate time in the oral cavity was tested and was found to be around 1 minute. It was concluded that rapidly disintegrating tablets with proper hardness rapidly disintegrates in the oral cavity with enhanced dissolution rate.

Modi a., Tayade P. et al., (2006) studied the enhancement of dissolution profile by solid dispersion technique.

Mukesh G. *et al*., (2006) Formulates mouth dissolving tablet of Nimesulide. Granules containing nimesulide, camphor, crospovidone and lactose were prepared by wet Direct Compression technique. Camphor was sublimed from the dried granules by exposure vacuum. The porous granules were then compressed and evaluated. The result for obtaining a rapidly disintegrating dosage forms, tablets should be prepared using an optimum concentration of camphor and a higher percentage of crospovidone.

Patil M.B. et al., (2006) Formulated and evaluated ondansetron HCl directly compressed mouth dissolving tablet.

Popa G. and Gafitanu E. et al., (2000) studied oral disintegrating tablets as a new modern solid dosage form. FuY and Park K. studied the application of poly acrylic super porous hydro gel micro particles as a superdisintegrant in fast dissolving tablets. Direct compression is the easiest way of manufacturing tablets. Super porous hydrogel has numerous porous connected together to form open channel structure. Water is absorbed in to dried super porous hydrogel by capillary wetting rather than by diffusion. It swells fast with the swelling ratio more than 100 times with in minutes. Fast dissolving tablets prepared by direct compression in the presence of super porous hydrogel micro particles disintegrate very quickly (Park).

Prameela Rani A.,Kanakadurga N. et al., (2010) Formulation and evaluation of taste smasked oro dispersible tablets of Montelukast sodium. The purpose of this research was to mask the intensely bitter taste of montelukast sodium adopting inclusion complex formation array using betacyclodextrin by kneading method. Through this research work we have formulated and evaluated ODTs (oro dispersible

tablets) by attending the optimization of taste masked inclusion complex of drug with β-CD at various ratios**.**

Roop K. Khar, *et al.,* (2001) Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. So, any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor's product and would translate into better compliance and therapeutic value for the patient. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability. This article reviews the earlier applications and methodologies of taste masking and discusses the most recent developments and approaches of bitterness reduction and inhibition for oral pharmaceuticals.

Sajal Kumar Jha *et al.,* (2006) In present investigation Haloperidol was well absorbed after oral dose. There is a first pass metabolism leading to a reduced bioavailability which in need of dosage forms development. Melt-in-mouth tablets of Haloperidol are prepared by direct compression method using superdisintegrants such as croscarmellose sodium, sodium starch glycollate, crospovidone. Resultant; various formulations reveals the improved bioavailability.

Sammour O.A., Hammaad M.A., Megrap N.A., Zidan A.S. et al., (2006) Carried out the formulation and optimization of mouth dissolving tablets containing rofecoxcib.

Seagar. H. et al., (1995) studied new drug delivery products and , for and process technology of zydis for preparing fast dissolving tablets. zydis formulation consists of drug physically entrapped or dissolved within the matrix of fast dissolving carrier matriel. Seager studied the matrix characteristics,packaging,moisture pickup properties etc.and concluded that the overall dissolution rate of water insoluble drug from Zydis dosage form from the fluids of GIT is similar to that from oral dosage form and bioavailability of water insoluble substances is equivalent to that of high quality tablets and hard gelatin capsules.

Shirwailkar A.A. *et al.,* (2004) Formulated Atenolol fast disintegrating tablet using three superdisintegrants croscarmellose (Ac-di-sol), crospovidone (Polyplasdone) and sodium starch glycollate. Ac-di-sol proved to be the best among the three and showed satisfactory results.

Shirwaikar A. *et al.,* (2005) Carried out formulation of fast dissolving tablets of Granisetron Hydrochloride using super disintegrants by employing Direct compression method, Formulation containing crospovidone and croscarmellose sodium displayed shortest disintegrate time compare to other disintegrants.

Shishs and bhatti A. et al., (Aug 2006) Made of fast dissolving tablets of diazepam at university Dept. of pharm. Sciences, Punjab university Chandigarh.

Sreenivas S. A. *et al.*, (2006) Carried out formulation and evaluation of mouth disintegrating tablets of Ondansetron hydrochloride by direct compression method, by using disintegrates like crospovidone, croscarmellose sodium, pregelatinized starch, sodium starch glycolate that 10% disintegrate concentration is suitable for the preparationof Ondansetron hydrochloride and tablets containing disintegrates crosspovidone and crosscarmellose sodium are the best.

Van Schaick.et al., (2003) Did the pharmacokinetic comparision of fast disintegrating and conventional tablet formulation of resperidone in healthy volunteers and found that in healthy subjects , a tablets was equivalent to a single administration of two 0.5 mg conventional tablet .

Venkatalakshmi R. et al., (2009) Granisetron hydrochloride 200 mg mouth dissolving tablet was prepared by sodium Starch glycolate, Cros carmellose sodium,Cros povidone at various concentration and sucralose, aspartame used as sweetening agent. All the formulation were prepared by direct compression method.

Drug and Excipients profile

5 DRUG AND EXCIPIENTS PROFILE

5.1. DRUG PROFILE

(Moffat A.C, 2004;USP 2009; Indian Pharmacopoeia, 2007;www.pharmpedia.com; CIMS,2009; www.drugs.com)

Synonyms:

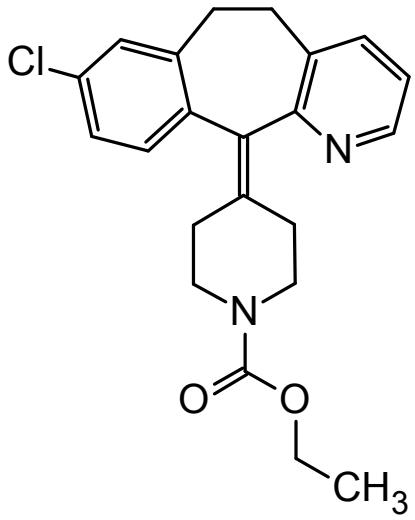
Loratadina [Spanish]

Loratadinum [latin]

Proprietary names:

Aerotina, alarin, alavert, biloina, claritin-d, loritine, lorfast, loraver.

Chemical structure:



Molecular formula: $C_{22}H_{23}ClN_2O_2$

Molecular weight: 382.88

Iupac name:

Ethyl 4-{13-chloro-4-azatricyclo[9.4.0.0^{3,8}]pentadeca-1(11),3,5,7,12,14-hexaen-2-ylidene}piperidine-1-carboxylate

Indications :

A self-medication that is used alone or in combination with pseudoephedrine sulfate for the symptomatic relief of seasonal allergic rhinitis. Also used for the symptomatic relief of pruritus, erythema, and urticaria associated with chronic idiopathic urticaria in patients (not for children under 6 unless directed by a clincian).

Appearance:

A white or almost white, characteristic, fine powder.

Solubility:

Freely soluble in acetone, Chloroform,methanol,toluene,insoluble in water.

Melting point:

134-136ºC

Metabolism:

Hepatic

Toxicity:

somnolence, tachycardia, and headache LD_{50}=mg/kg (orally in rat)

Serious side effects:

- fast or uneven heart rate;
- feeling like you might pass out;
- jaundice (yellowing of your skin or eyes); or

- seizures (convulsions).

Less serious side effects may include:

- headache;
- nervousness;
- feeling tired .

Bioavailability:

Available about 50 to 60%. Depends partly on dosage form. Bioavailability of mouth dissolving tablet is relatively more, than other oral dosage forms.

Half–life:

8.4 hours

Volume of distribution:

4.5 to 8 L/kg

Clearance:

The total oral clearance from plasma is 6 to 10mL/min/h

Protein binding:

97-99%

Dose:

10 mg to 50 mg daily with a maximum of 300mg daily in divided doses.

Pharmacodynamic:

Loratadine is a long acting second generation antihistamine that is similar in structure to cyproheptadine and azatadine. The pharmacology of loratadine is similar to other antihistamines, but unlike other H_1-blockers, loratidine is shown to exhibit

competitive, specific, and selective antagonism of H_1 receptors. The exact mechanism of this interaction is unknown, but disposition of the drug suggests that loratadine's prolonged antagonism of histamine may be due to the drug's slow dissociation from the receptor or the formation of the active metabolite, desloratadine. Loratadine does not penetrate the CNS effectively and has a low affinity for CNS H_1-receptors.

Mechanism of Action:

Loratadine competes with free histamine and exhibits specific, selective peripheral H_1 antagonistic activity. This blocks the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms (eg. nasal congestion, watery eyes) brought on by histamine. Loratadine has low affinity for cholinergic receptors and does not exhibit any appreciable alpha-adrenergic blocking activity in-vitro. Loratadine also appears to suppress the release of histamine and leukotrienes from animal mast cells, and the release of leukotrienes from human lung fragments, although the clinical importance of this is unknown.

Pharmacology and Uses:

Loratadine is long acting peripheral H_1-receptor antagonist. It is mainly used as antihistaminic drug.

5.2. EXCIPIENT PROFILES

I. SODIUM STARCH GLYCOLLATE

(Raymond C. Rowe, 2003)

Nonproprietary names:

BP Sodium starch glycollate; PhEur Carboxymethylamylum natricum; USPNF Sodium starch glycollate.

Synonyms:

Carboxymethyl starch, sodium salt; *Explosol*; *Explotab*; *Glycolys*; *Primojel*; starch carboxymethyl ether, sodium salt.

Chemical name:

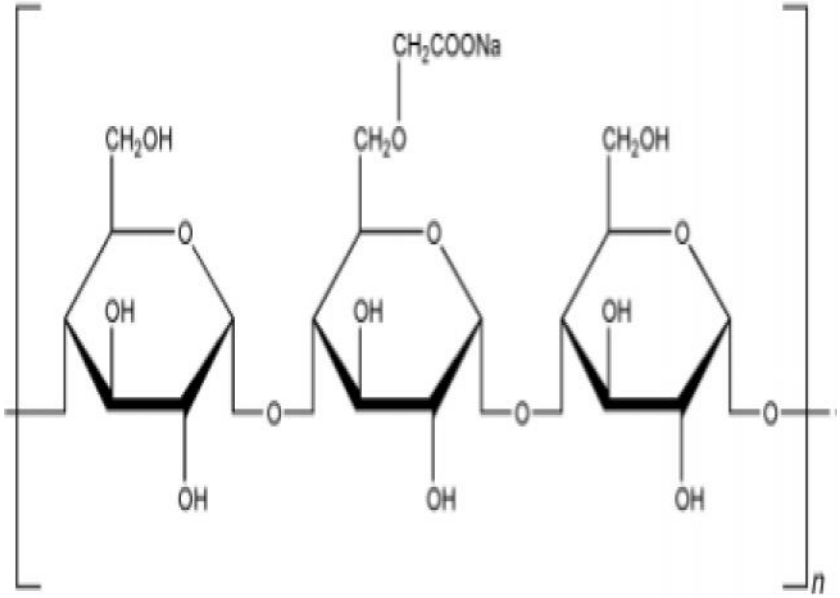
Sodium carboxymethyl starch

Empirical formula and molecular weight:

The USPNF 23 states that sodium starch glycollate is the sodium salt of a carboxymethyl ether of starch, containing 2.8 to 4.2% sodium.

The PhEur 2005 describes three types of material Types A and B occurs as the sodium salt ofa cross-linked partly *O*-carboxymethylated potato starch, containing 2.8 to 4.2% and 2.0 to 3.4%of sodium respectively. Type C is the sodium salt of a cross-linked by physical dehydration, partly *O*-carboxymethylated starch containing 2.8–5.0% sodium. The JP, PhEur and USPNF monographs have been Harmonized for Type A and Type B variants Sodium starch glycollate may be characterized by the degree of substitution and cross linking. The molecular weight is typically 5 × 105 - 1 × 106.

Structural formula:



Functional category:

Pharmaceutical excipients, tablet and capsule disintegrate.

Applications in pharmaceutical formulation or technology:

Sodium starch glycollate is widely used in oral pharmaceuticals as a disintegrate in capsule and tablet formulations . It is commonly used in tablets prepared by either direct compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegrate occurs by rapid uptake of water followed by rapid and enormous swelling. Although the effectiveness of many disintegrates is affected by the presence of hydrophobic excipients such as lubricants, the disintegrate efficiency of sodium starch glycollate is unimpaired. Increasing the tablet compression pressure also appears to

have no effect on disintegrate time. Sodium starch glycollate has also been investigated for use as a suspending vehicle.

Description:

Sodium starch glycollate is a white to off-white, odorless, tasteless, free-flowing powder. The PhEur 2005 states that it consists of oval or spherical granules, 30 - 100 μm in diameter, with some less-spherical granules ranging from 10 - 35 μm in diameter.

Typical properties

Acidity/alkalinity:

pH = 3.0–5.0 or pH = 5.5–7.5 for a 3.3% w/v aqueous dispersion.

Ash:

= –15% for *Explotab*

Density (bulk):

0.756 g/cm^3; 0.75 g/cm^{3}for *Explotab*; 0.81 g/cm^3 for *Primojel*; 0.67 g/cm^3 for *Tablo*.

Density (tapped):

0.945 g/cm^3; 0.88 g/cm^{3,} for *Explotab*.

Density (true):

1.443 g/cm^3; 1.51 g/cm^3 for *Explotab*.

Melting point:

Does not melt, but chars at approximately 200°C.

Particle size distribution:

100% of particles less than 106 μ cm in size. Average particle size is 35–55 μ cm for *Explotab*.

Solubility:

Sparingly soluble in ethanol, practically insoluble in water. At a concentration of 2%w/v sodium starch glycollate disperses in cold water and settles in the form of a highly hydrated layer.

Specific surface area:

0.24 m^2/g; 0.202 m^2/g for *Explotab*;

Swelling capacity:

In water, sodium starch glycollate swells to up to 300 times its volume.

Viscosity (dynamic):

=¼200 m Pa s (200 cP) for a 4% w/v aqueous dispersion. Viscosity is 4.26 m Pa s for a 2% w/v aqueous dispersion.

Stability and storage conditions:

Tablets prepared with sodium starch glycollate have good storage properties. Sodium starch glycollate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of sodium starch glycollate remain unchanged for up to 3 - 5 years if it is stored at moderate temperatures and humidity.

Incompatibilities:

Sodium starch glycollate is incompatible with ascorbic acid.

Method of manufacture:

Sodium starch glycollate is a substituted derivative of potato starch. Typically, commercial products are also cross-linked. Starch is carboxymethylated by reacting it with

sodium chloroacetate in an alkaline medium followed by neutralization with citric acid or some other acid. Cross linking may be achieved either by physical methods or chemically by using reagents such as phosphorusoxytrichloride or sodium trimetaphosphate.

Safety:

Sodium starch glycollate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

Handling precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium starch glycollate may be irritant to the eyes; eye protection and gloves are recommended. A dust mask or respirator is recommended for processes that generate a large quantity of dust.

Regulatory acceptance:

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets).Included in non-parentral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

Comments:

The physical properties of Sodium starch glycollate, and hence its effectiveness as a disintegrate, are affected by the degree of cross linkage, extent of carboxymethylation, and purity.

II. CROSCARMELLOSE SODIUM [AC-DI-SOL] *(Raymond C. Rowe et al., 2003)*

Nonproprietary name:

USP NF Croscarmellose sodium

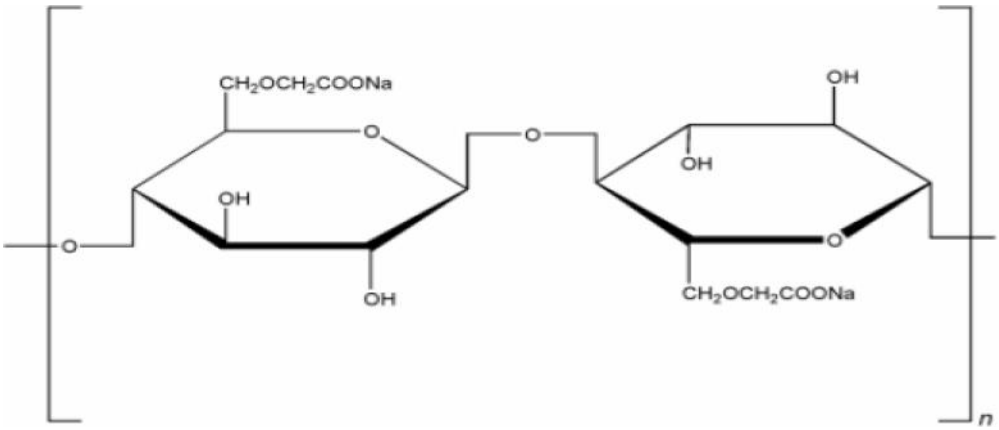
Synonyms:

AC-Di-sol; Cross-linked carboxymethyl cellulose sodium,Modified cellulose gum, Nymcel 25x;Primellose, Solutab.Chemical name Cellulose, Carboxymethyl ether, sodium salt, cross linked.

Molecular weight:

Typical molecular weight: 90,000 - 700000

Structural formula:



Functional category:

Tablet and Capsule disintegrate

Description:

Croscarmellose sodium occur odorless, white colored powders

Typical properties

Particle size distribution:

Not more than 2% retained on#200 (73.7m m)mesh and not more than 10% retained on a #325 (44.5mm) mesh for Ac-Di-sol.

Solubility:

Insoluble in water although Croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water

Stability and storage conditions:

Croscarmellose sodium is a stable though hygroscopic material. Amodel tablet formulation prepared by direct compression with Croscarmellose sodium as disintegrate, showed no significant difference in drug dissolution after storage at 30^{o} C for 14 months. Croscarmellose sodium should be stored in well-closed container in a cool, dry place.

Incompatibilities:

The efficacy of disintegrates, such as croscarmellose sodium maybe slightly reduced in tablet formulations prepared by either wet direct compression or direct compression process, which contain hygroscopic excipients as sorbitol.

Application in pharmaceutical formulation or technology:

Croscarmellose sodium is used in oral Pharmaceutical formulation as a disintegrate for capsules, tablets and granules. In tablet formulation croscarmellose sodium may be used in both direct compression and wet direct compression processes., when used in wet direct compression the croscarmellose sodium is best added in both the wet and dry stages of the process intra and extra granularly so that wicking and swelling ability of disintegrate is best

utilized, concentrations of up to 5% w/w of croscarmellose sodium may be used as tablet disintegrate although normally 2% is used in direct compression.

III. CROSPOVIDONE *(Raymond C. Rowe, 2003)*

Nonproprietary names:

BP Crosspovidone; PhEur Crospovidonum; USPNF Crospovidone.

Synonyms:

Crosslinked povidone, E1202 Kollidon CL,\XL-10, polyvinyl polypyrrolidone PVP,1-vinyl 2 pyrrolidone homopolymer

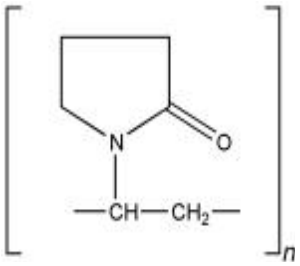
Chemical name:

1- Etheny1-2 pyrrolidinone homopolymer

Empirical formula:

$[C_6H_9NO]_n$

Structural formula:



Molecular weight;

> 1000000

Functional category:

Tablet disintegrate

Description:

Crospovidone is white to creamy white, finely divided free flowing. Practically tasteless, odorless or nearly odorless, hygroscopic powder.

Solubility:

Practically insoluble in water and most common organic solvents

Typical properties

Acidity / Alkalinity pH:

5.0-8.0(1%w/v aqueous slurry)

Density:

1.22 g/cm^3

Bulk density:

Polyplasdone XL10 – 0.416 g/cm^3

Moisture content:

Maximum moisture sorption is approximately60%Polyplasdone XL-10- 5.0 % maximum.

Compressibility (Carr index):

Polyplasdone XL -10-30%

Particle size distribution:

Less than 74 μm for Polyplasdone XL-10

Specific surface Area:

Polyplasdone XL-10 1.2-1.4m^2/g

Stability and storage condition:

Since Crosspovidone is hygroscopic, it should be stored in an airtight container in cool and dry place.

Application in pharmaceutical formulation or technology:

Crospovidone is a water-insoluble tablet disintegrates and dissolution agent used at 2-5% concentration in tablets prepared by direct compression or wet and dry Direct Compression, It rapidly exhibits high capillary activity and Pronounced hydration capacity with little tendency to form gels. The particle size of crospovidone strongly influences disintegrate of tablets. Larger particle provide a faster disintegrate than smaller particles. Crospovidone can also be used as solubility enhancer.

Incompatibilities:

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, Crospovidone may form molecular adduct with some materials.

IV. AEROSIL *(Raymond C. Rowe, 2003)*

Nonproprietary names:

BP Colloidal anhydrous silica; PhEur Silica colloidal is an hydrica; USPNF Colloidal silicon dioxide.

Synonyms:

Aerosil; *Cab-O-Sil*; *Cab-O-Sil M-5P*; colloidal silica; fumed silica; light anhydrous silicic acid; silicic anhydride; silicon dioxide fumed; *Wacker HDK*.

Chemical name and cas registry number:

Silica [7631-86-9]

Empirical formula:

SiO_2

molecular weight:

60.08

Functional category:

Adsorbent; anti caking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrate; thermal stabilizer; viscosity-increasing agent

Applications in pharmaceutical formulation or technology:

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products; its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tablet. Uses of colloidal silicon dioxide as follows;

Use in concentration (%)

Aerosols 0.5 to 2.0

Emulsion stabilizer 1.0 to 5.0

Glidant 0.1to 0.5

Suspending and thickening agent 2.0 - 10.0

Aerosil is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations with other ingredients of similar refractive index, transparent gels may be formed. The degree of viscosity increase depends

on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than non polar liquids). Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity.

Description:

Aerosil is submicroscopic fumed silica with a particle size of about15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, nongritty amorphous powder.

Typical Properties

Acidity/alkalinity:

pH = 3.5 - 4.4 (4% w/v aqueous dispersion)

Density (bulk):

0.029 - 0.042 g/cm^3

Density (tapped):

0.05 g/cm^3

Flow ability:

35.52% (Carr compressibility index)

Solubility:

Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.

Specific surface area:

200 - 400 m^2/g (Stroehlein apparatus, single point); 50 - 380 m^2/g (BET method). Several grades of colloidal silicon dioxide are commercially available, which are produced by modifying the manufacturing process.

Stability and storage conditions:

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. Aerosil powder should be stored in a well-closed container. Some grades of colloidal silicon dioxide have hydrophobic surface treatments that greatly minimize their hygroscopity.

Incompatibilities:

Incompatible with diethylstilbestrol preparations

Method of manufacture:

Aerosil is prepared by the vapor hydrolysis of chlorosilanes, such as silicon tetrachloride, at 1800°C using a hydrogen–oxygen flame.

Safety:

Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipients. However, intraperitoneal and subcutaneous injection may produce local tissue reactions and/orgranulomas. Therefore it is not being administered parental.

LD_{50} (rat, IV) 15 mg/kg

LD_{50} (rat, oral) 3.16 g/kgs

Handling precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Precautions should be taken to avoid inhalation of colloidal silicon dioxide.

VI. MANNITOL **(**Raymond C. Rowe, 2003)

Nonproprietary Names:

BP Mannitol; JP D-Mannitol; PhEur Mannitolum; USP Mannitol

Synonyms:

Cordycepic acid;*C*PharmMannidex*; E421; manna sugar; D-mannite; mannite; Mannogem;Pearlitol.

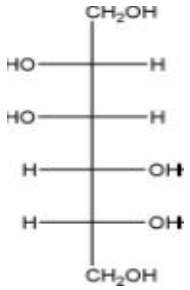
Chemical name:

D-Mannitol

Empirical formula and molecular weight:

$C_6H_{14}O_6$182.17

Structural formula:



Functional category:

Diluents; Diluents' for Lyophilized preparations; Sweetening agent; Tablet and Capsule diluents; Tonicity agent.

Applications in pharmaceutical formulation or technology:

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluents (10 - 90% w/w) in tablet

formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients .Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations.

Description:

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Mannitol shows polymorphism.

Typical properties

Density (bulk):

0.430 g/cm^3 for powder; 0.7 g/cm^3 for granules.

Density (tapped):

0.734 g/cm^3 for powder; 0.8 g/cm^3 for granules.

Density (true):

1.514 g/cm^3

Dissociation constant:

p*K*a = 13.5 at 18°C

Flash point:

<150°C

Flow ability:

Powder is cohesive, granules are free flowing.

Melting point:

166–168°C

Particle size distribution:

Pearlitol 300 DC maximum of 0.1% greater than 500 μ˘m and minimum of 90% greater than 200 μ+m in size;

Pearlitol 400 DC maximum of 20% greater than 500 μm and minimum of 85% greater than 100 μm in size;

Average particle diameter is 250 μm for *Pearlitol 300 DC*, 360 μm for *Pearlitol 400 DC* and520 μm for *Pearlitol 500 DC*.

Solvent solubility at 20°C:

Soluble in Alkalis ,Ethanol (95%) 1 in 83, Practically in soluble in Ether and soluble 1 in 18 in Glycerin

Specific surface area:

0.37–0.39 m^2/g

Storage conditions:

The bulk material should be stored in a well-closed container in a cool, dry place.

Method of manufacture:

Mannitol may be extracted from the dried sap of manna and other natural sources by means of hot alcohol or other selective solvents. It is commercially produced by the catalytic or electrolytic reduction of monosaccharide's such as mannose and glucose.

Handling precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Mannitol may be irritant to the eyes; eye protection is recommended.

VII. MICROCRYSTALLINE CELLULOSE **(**Raymond C. Rowe, 2003)

Nonproprietary name:

BP Microcrystalline cellulose; PhEur Cellulose microcrystalline; USPNF Microcrystalline cellulose.

Synonyms:

Avicel, cellulose gel, crystalline cellulose,E460, Emcocel, Fibrocel, Tabulose.

Chemical Name:

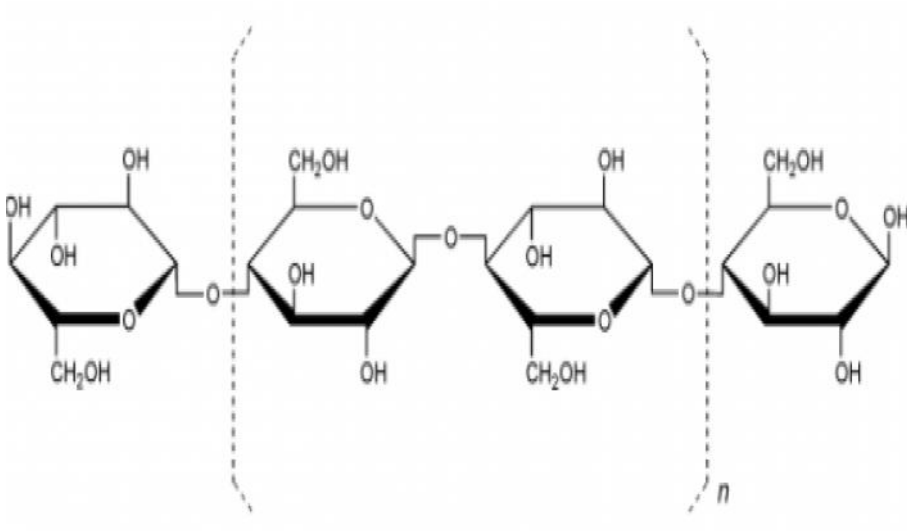
Cellulose

Empirical formula:

$(C_6H_{10}O_5)_n$, Where n~220.

Molecular Weight: 36000.

Structural Formula:



Functional category:

Adsorbent, Suspending agent, tablet and capsule diluents, tablet disintegrate.

Description:

Microcrystalline cellulose is purified; partially depolymerized cellulose that occurs as a white colored, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different size particle grades which have different properties and application.

Applications in pharmaceutical formulation or technology:

Microcrystalline cellulose is widely used in pharmaceutical is primarily as diluents in oral tablet and capsule formulations. Where it is used in both wet Direct Compression and direct compression processes. In addition to its use as a diluents. Microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tablet.

Typical Properties

Bulk density:

(MCC pH102) = 0.307 g/cm^3

Tapped density:

(MCC pH102) = 0.307 g/cm^3

Density:

(MCC pH102) = 1.554 g/cm^3

Melting point:

260-270^{0}C

Particle size:

(MCC pH102) = 100mm

Particle size distribution:

Typical mean particle size is 20 to 200mm Different grades have different nominal mean particle size (pH102) 100mm

Moisture content:

Less than 5% w/w However different grade may contain varying amount of water Microcrystalline cellulose is hygroscopic (pH102) = 3.315%.

Solubility:

Slightly soluble in 5%w/v Sodium hydroxide solution, practically insoluble in water dilutes acids and most organic solvent.

Incompatibilities:

Incompatible and strong oxidizing agents.

Stability and storage conditions:

Microcrystalline cellulose is a stable, though hygroscopic material the bulk material should be stored in well closed container in a cool and dry place.

VIII. ASPARTAME **(**Raymond C. Rowe, 2003)

Nonproprietary names:

BP Aspartame; PhEur Aspartamum; USPNF Aspartame

Synonyms:

3-Amino-*N*-(aì-carboxyphenethyl) succinamic acid *N*-methyl ester; 3-amino-*N*-(aìmethoxycarbonylphenethyl) succinamic acid; APM; aspartyl phenylamine methyl ester;*Canderel*; E951; *Equal*; methyl *N*-a_-L-aspartyl-L-phenylalaninate; *NutraSweet*; *Pal Sweet*; *Pal Sweet Diet*; *Sanecta*; SC-18862; *Tri-Sweet*.

Chemical Name:

N-aò-L-Aspartyl-L-phenylalanine 1-methyl ester.

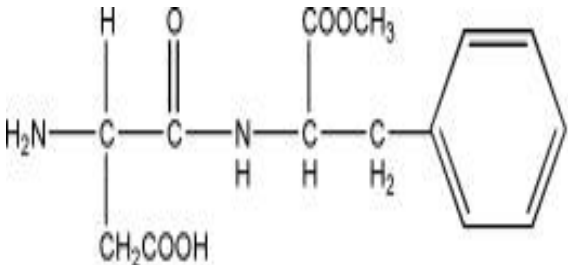
Empirical Formula

$C_{14}H_{18}N_2O_5$

Molecular Weight:

294.31

Structural Formula:



Functional Category:

Sweetening agent.

Applications in Pharmaceutical Formulation or Technology:

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets,1,2 powder mixes, and vitamin preparations. It enhances flavor systems and can be used to

mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose. Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value 1 g provides approximately 17 kJ (4 kcal). However, in practice, the small quantity of aspartame consumed provides a minimal nutritive effect. Therapeutically, aspartame has also been used in the treatment of sickle cell anemia.

Description:

Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

Typical Properties

Acidity/alkalinity:

pH = 4.5–6.0 (0.8% w/v aqueous solution).

Bonding index:

0.8 × 102 (worst case); 2.3 × 102 (best case).

Flow ability:

44% (Carr compressibility index)

Density (bulk):

0.5–0.7 g/cm^3 for granular grade;0.2–0.4 g/cm^3 for powder grade.

Density (tapped):

0.29 g/cm^3 (Spectrum Quality Products)4

Density (true):

1.347 g/cm^3

Effective angle of internal friction:

43.0°

Melting point:

246–247°C

Solubility:

Slightly soluble in Ethanol (95%); sparingly soluble in Water. At 20°C the solubility is 1%w/v at the iso-electric point (pH 5.2). Solubility increases at higher temperature and at more acidic pH, e.g., at pH 2 and 20°C solubility is 10% w/v.

Stability and Storage Conditions:

Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl-L-phenylalanineand 3-benzyl-6-carboxymethyl-2,5-diketopiperazine. A third-degradation product is also known, ßæ-L-aspartyl-L-phenylalaninemethyl ester. For the stability profile at 25°C in aqueous buffers, Stability in aqueous solutions has been enhanced by the addition of cyclodextrins, and by the addition of polyethylene glycol 400 at pH 2.7 However, at pH 3.5 - 4.5 stability is not enhanced by the replacement of water with organic solvents. Aspartame degradation also occurs during prolonged heat treatment; losses of aspartame maybe minimized by using processes that employ high temperatures for a short time followed by rapid cooling. The bulk material should be stored in a well-closed container, in a cool, dry place.

Incompatibilities:

Differential scanning colorimetry experiments with some directly compressible tablet excipients suggests that aspartame is incompatible with dibasic calcium phosphate

and also with the lubricant magnesium stearate. Reactions between aspartame and sugar alcohols are also known.

Method of Manufacture:

Aspartame is produced by coupling together L-phenylalanine (or L-phenylalanine methylester) and L-aspartic acid, either chemically or enzymatically. The former procedure yields both the sweet α-aspartame and non sweet β-aspartame from which the α-aspartame has to be separated and purified. The enzymatic process yields only α°-aspartame.

Safety:

Aspartame is widely used in oral pharmaceutical formulations, beverages, and food products as an intense sweetener and is generally regarded as a nontoxic material. However, the use of Aspartame has been of some concern owing to the formation of the potentially toxic metabolites methanol, aspartic acid, and phenylalanine. Of these materials, only phenylalanine is produced in sufficient quantities, at normal aspartame intake levels, to cause concern. In the normal healthy individual any phenylalanine produced is harmless, however it is recommended that aspartame be avoided or its intake restricted by those persons with phenylketonuria. The WHO has set an acceptable daily intake for aspartame at up to 40 mg/kg body-weight. Additionally, the acceptable daily intake of diketopiperazine (an impurity found in Aspartame) has been set by the WHO at up to 7.5 mg/kg body-weight. A number of adverse effects have been reported following the consumption of aspartame, particularly in individuals who drink large quantities (up to 8 liters per day in one case) of Aspartame-sweetened beverages. Reported adverse effects include headaches. Grand mal seizure; memory loss; gastrointestinal symptoms; and dermatological symptoms. Although

aspartame has been reported to cause hyperactivity and behavioral problems in children, a double-blind controlled trial of 48 preschool-age children fed diets containing a daily intake of 38 ± 13 mg/kg body-weight of aspartame for 3 weeks showed no adverse effects attributable to aspartame, or dietary sucrose, on children's behavior or cognitive function.

Handling precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Measures should be taken to minimize the potential for dust explosion. Eye protection is recommended.

Regulatory status:

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral powder for reconstitution, buccal patch, granules, film-coated, and tablets).Included in non parental medicines licensed in the UK .Included in the Canadian List of Acceptable Non-medicinal Ingredients.

Related substances:

Alitame.

5.2.6. MAGNESIUM STEARATE *(Raymond C.R., et al., 2003)*

Nonproprietary names:

BP **:** Magnesium stearate

JP **:** Magnesium stearate

PhEur **:** Magnesii stearas

USPNF **:** Magnesium stearate

Synonyms:

Magnesium octa decanoate, Magnesium salt.

Chemical name and CAS registry number:

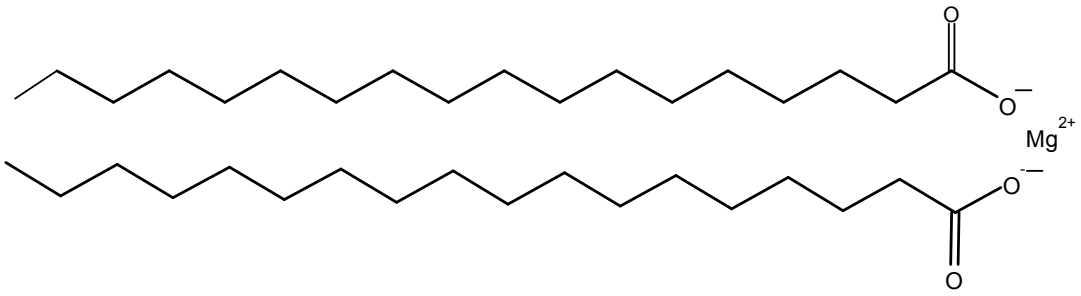
Octa decanoic acid magnesium salt [557-04-0]

Functional category : Tablet and capsule lubricant

Empirical formula : $C_{36}H_{70}MgO_4$

Molecular weight : 591.3

Structural formula:



Description:

It is a fine, white, precipitated or milled, impalpable powder of low bulk density and having a faint odor of stearic acid, characteristic taste.

Solubility:

It is insoluble in water, ethanol and ether. It can slightly soluble in warm ethanol and benzene.

Stability and storage conditions:

Stable, Store in a well closed container in a cool, dry place.

Materials and Equipment

6. MATERIALS AND METHODS

Table 6.1: List of materials and their suppliers

S. No.	Materials	Source
1	Loratadine	Sun pharma, Mumbai
2	Sodium starch glycollate	Sun pharma, Mumbai
3	Crospovidone	Sun pharma, Mumbai
4	Croscarmellose sodium (Ac-di-sol)	Sun pharma, Mumbai.
5	Aerosil	LOBA chemie P.Ltd. Mumbai.
6	Magnesium stearate	MADRAS pharmaceuticals, Chennai
7	Mannitol	MADRAS pharmaceuticals, Chennai
8	Microcrystalline cellulose	MADRAS pharmaceuticals, Chennai
9	Aspartame	Orchid pharmaceuticals, Chennai.
10	Strawberry (flavor)	Orchid pharmaceuticals,Chennai

Table 6.2: List of equipments with model/make

Sl. No.	Name of the Instruments	Make	Model
1	Electronic Balance	Shimadzu, Japan	BL- 200H.
2	UV-Visible Spectrophotometer	Shimadzu, Japan	1700
3	16 station rotary tablet compression machine	Cadmach, Ahmedabad, India	JMD-4-8
4	Hardness Tester	Monsanto	---
5	Roche Friability Tester	Veego scientifics, Mumbai	VET-DV
6	FTIR Spectrophotometer	Perkin elmer-Pharmaspec-1	----
7	USP, Type II Dissolution Test Apparatus	Veego scientifics, Mumbai	VDA – 8DR.
8	USP, Disintegrate test apparatus	Veego scientifics, Mumbai	VTD-DV
9	Digital pH Meter	Elico scientifics, Mumbai	L1610
10	Hot air oven	Prescision scientific co., Chennai	P-1401
11	Vernier Calipers	Indolabs, Chennai	---
12	Humidity Chamber	Labtech, Ambala	----
13	Tap Density Apparatus	Indolabs, Chennai	VTAP-M-2
14	Melting Point Test Apparatus	Prescision scientific co., Chennai	---
15	Standard sieve	Jayant scientific, India	---

Experimental work

7.EXPERIMENTAL WORK

7.1 Preformulation study

7.1.1 Identification of drug

7.1.1.1 By FTIR spectroscopy

(Moffat A.C., 2004;Indian Pharmacopoeia, 2007;www.pharmpedia.com)

The infrared spectrum of Loratadine and polymers were recorded by using FT-IR (Schimadzu 8400 SCCE). A small quantity of sample was mixed with equal quantity of potassium bromide and placed in sample cell to record its IR spectra.

7.1.1.2. By Melting point

Melting point is the one of important parameter for identification of pure drug and it is tested by using melting point apparatus.

7.1.2. Physiochemical parameter

7.1.2.1. Organoleptic properties *(Indian Pharmacopoeia, 2007)*

*T*he general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Included in are tablet's sizes, shape, color, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking which was observed visually.

7.1.2.2. Solubility profile

Solubility is a useful parameter mainly for poorly soluble drugs. Bioavailability problems are often present, when the solubility of a drug is less than 10 mg/ml over the pH range 1-8. The solubility of drug was recorded by using various descriptive

terminology specified in Indian pharmacopoeia, 2007. In this maximum amount of solvent required to dissolve the solute was determined.

7.1.2.3. Loss on drying *(Indian Pharmacopoeia, 2007)*

Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified condition. The accurately weighed 1gm of sample was transferred in glass-stoppered, hallow weighing bottle and accurately weighed the bottle. The bottle was transferred in oven and substance was dried at 105°C for 3 hours. The bottle was removed from oven and reweighed; loss on drying was calculated by following equation,

$$\text{Loss on drying} = \frac{\text{Initial weight of substance} - \text{Final weight of substance}}{\text{Initial weight of substance}} \times 100$$

7.1.3. Analytical methods

7.1.3.1. Determination of absorption maximum in Solvents

10 mg of Loratadine was weighed and transfer in to 3 individual 100 ml standard flask and made up to the mark with methanol, 0.1N HCL and Phosphate Buffer pH 6.4 separately. From the above solution took each 1 ml from each solution and make up with 10 ml standard flask to get the concentration of 10 µg/ ml of each solution. Each blank was kept separately and scan in the region 200 - 400 nm and determine the absorption maxima of drug in three solvents. 247.5 nm for 0.1N HCl, 275.0 nm for Methanol, 274.0 nm for Phosphate buffer 6.8.

7.1.3.2. Preparation of standard calibration curve of loratadine in solvents

A stock solution of Loratadine from the above solution and to get the concentration of 5 to 30 µg/ ml in three solvents and its obey the beer's law.

7.1.3.3. Determination of percentage purity of drug *(IP 2007)*

Accurately weighed 100 mg of loratadine was dissolved in little quantity of 0.1 N HCl and volume was adjusted to 100 ml with the same to prepare standard solution having concentration of 1000 µg/ ml. From the above solution, aliquots of 3 ml were transferred to 10 ml volumetric flasks and final volume was made to 10 ml with 0.1N HCl. Absorbance values of these solutions were measured against blank (0.1N HCl) at 275 nm using Shimadzu-1700 Pharmaspec UV-Visible spectrophotometer. The percentage purity of drug was calculated by using calibration graph method (least square method).

7.1.4. Determination of drug-polymer compatibility

7.1.4.1. By Fourier Transforms Infra-Red (FTIR) Spectroscopy

(Moffat A.C, 2004;Roberat M. Silverstein, 2003; Sajal kumar Jha, Divakar goli.2008)

Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the superdisintegrants. A physical mixture (1:1) of drug and superdisintegrants was prepared and mixed with suitable quantity of Potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to 400 cm^{-1} in a Parkin elmer-Pharmaspec-1 FTIR Spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and matching was done to detect any appearance or disappearance of peaks.

Parameters of I. R. Spectrum

Measuring Mode : % T (0-100%T)

Resolution : 4.0 cm^{-1}

Detector :Detector 1(2.8 mm/sec)

Apodization : HAPP – GENZEL

Gain :Auto

Wavelength : 4000 – 400 cm^{-1}

The drug superdisintegrants interaction was carried out using FT-IR (Parkin elmer-Pharmaspec-1). Individual IR spectra of drug and superdisintegrant as well as in combination were taken and compared to see if interaction has occurred or not. The above stated procedure is followed to record IR spectra.

7.1.4.2. By Differential Scanning Calorimetry Study (DSC) *(Chatwal G. R., 2007)*

In drug formulation it is essential to evaluate the possible interactions between the active principle and the superdisintegrants, as the choice of the superdisintegrants should be performed in relation to the drug delivery, to their compatibility with the same drug and to the stability of the final product. Loratadine powder was mixed with various superdisintegrants in the ratio of 1:1 and the resulting physical mixture was kept in sealed glass vials. Mixture should be examined under Nitrogen to eliminate oxidative and pyrolytic effect at a standard heating rate (2, 5 or 10^0C/minute) on DSC. Thermograms of pure drug are used as a reference.

Appearance or disappearances of one or more peaks in thermogram of drug with polymer are considered as an indication of interaction.

7.1.5. Formulation and characterization of powder blend

(Lachman L, 1991;Bankar G.S..1996)

Method

Accurate quantity of drug and all ingredients were weighed according to formula shown in Table 7.1 and powder except aerosil and magnesium sterate was blended homogeneously in mortor and pestel for 15 minutes. Prepared powder blend was passed through sieve No.#60. Finally aerosil and magnesium sterate passed through sieve No. #30 was added and further mixed for10 minutes. The powder blend was evaluated for angle of repose, bulk density, Tapped density, Compressibility Index and Hausner ratio.

7.1.5.1.

7.1.5.2. Angle of Repose

Angle of repose was determined using cylinder method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (q) was calculated using the formula

$$\Theta = \tan^{-1}(r/h)$$

Method

Weighted quantity of Loratadine was passed through funnel kept at height at 9 cm from base. The powder forms heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated.

Table 7.1: Standard Relationship between Angle of Repose (Θ) and Flow ability

Angle of repose (Θ)	Flowability
< 20	Excellent
20-30	Good
30-34	Passable*
> 40	Very poor

*Adding glidant for improving flow

7.1.5.2. Bulk density

Apparent bulk density (ρ_b) was determined by pouring blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined.The bulk density was calculated using the formula.

$$\rho_b = M/V_b \quad \text{(or)}$$

BD = Weight of the powder/Volume of the powder.

7.1.5.3. Tapped density

It was determined by placing a graduated cylinder, containing a known mass of drug excipients blend, which was tapped for a fixed time until the powder bed volume has reached a minimum. The minimum volume (V_t) occupied in the cylinder and the weight

(m) of the blend was measured. The tapped density (ρ_t) was calculated using the following formula.

$$\rho_t = m / V_t \quad \text{(or)}$$

TBD = Weight of the powder/Tapped volume of the powder

7.1.5.4. Compressibility Index

The simplest way for measurement of free flow of powder is compressibility, a indication of the case with which a material can be induced to how is given by compressibility index (I) which is calculated as follows

Carr's compressibility index (%) = [(TBD-BD)/ TBD x100

Table 7.2: Table shows standard values of Carr's index

Carr's index	Flowability
5-15	Excellent
12-16	Good
18-21	Fair Passable
23-35	Poor
33-38	Very poor
> 40	Very very poor

The value below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor Flow ability.

7.1.5.5. Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula;

Hausner's ratio= ρ_t/ρ_b

Where, ρ_t is tapped density and ρ_b is bulk density

A hausner's ratio less than 1.25 indicates good flow while greater than 1.5 indicates poor flow.

7.2. Formulation of Mouth Dissolving Tablet of Loratadine

Table 7.3: Formulated Composition of different Batches of Mouth Dissolving Loratadine Tablets

S. No.	Ingredients (mg/tab)	Formulation code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Loratadine	10	10	10	10	10	10	10	10	10
2	Croscarmellose sodium (Ac-di-sol)	4	6	8	-	-	-	-	-	-
3	Sodium starch glycollate(Explotab)	-	-	-	4	6	8	-	-	-
4	Crospovidone (Polyplasdone)	-	-	-	-	-	-	4	6	8
5	Microcrystalline cellulose	74	72	70	74	72	70	74	72	70
6	Mannitol	100	100	100	100	100	100	100	100	100
7	Aerosil	4	4	4	4	4	4	4	4	4
8	Aspartame	6	6	6	6	6	6	6	6	6
9	Magnesium stearate	2	2	2	2	2	2	2	2	2
10	Strawberry flavour	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
11	Total	200	200	200	200	200	200	200	200	200

7.2.1. Preparation of mouth dissolving loratadine tablets

Method

The mouth dissolving tablets were prepared by direct compression method with the use of three different superdisintegrants namely Croscarmellose sodium, Sodium starch glycolate , Crospovidone in the ratio of 5:2, 5:3 and 5:4. Microcrystalline cellulose, Mannitol was used as a diluents as and mixture of Aerosil and Magnesium sterate (2:1) was used as a glidant and lubricant respectively. The composition of mouth dissolving formulation was shown in Table 7.3.

Accurate quantity of drug and all ingredients were weighed according to formula shown in Table 7.3 and powder except Aerosil and Magnesium sterate was blended homogeneously in mortor and pestle for 15 minutes. Prepared powder blend was passed through sieve no. #60. Finally Aerosil and Magnesium sterate passed from sieve no. #30 added and was further mixed for10 minutes.

Accurately weighed 200 mg homogeneously mixed powder blend was fed manually and compressed with constant compression force and hardness on 16 stations Cadmach tablet compression machine with 9 mm, breakthrough, and flat faced punches. Total nine formulations were prepared.

7.3. Evaluation of Loratidine MDTs

7.3.1. Appearance

The tablets were visually observed for capping, chipping and lamination.

7.3.2 Weight Variation

Method

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight.

Table 7.4: Specifications of % weight variation allowed in tablets as per indian pharmacopoeia

Average Weight of Tablet	% Deviation Allowed
80 mg or less	10
More than 80 mg but less that 250 mg	7.5
250 mg or more	5

7.3.3 Thickness uniformity

Method

Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

7.3.4 Hardness *(Lachman L,1991; Bankar G.S.,1996)*

Hardness or tablet crushing strength (Fo) the force required to break a tablet in a diametric compression was measured using Monsanto Hardness Tester.

For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the

tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2 .

7.3.5 Friability *(Lachman L,1991; Bankar G.S.,1996)*

Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and roping the tablets ata height of 6 inches in each revolution. Preweighed sample of tablets was placed in the Friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed, the friability (F) is given by the formula.

% F = (Initial wt. - Final wt. / Initial wt.) x 100.

7.3.6.Content uniformity *(Indian pharmacopoeia,2007;www.pharmpedia.com)*

The Loratadine content in the tablets was estimated as follows.

Method

20 tablets were finely powdered and weight equivalent to 10 mg of Loratadine was dissolved in 100 ml of methanol and assayed for drug content using UV-Visible spectrophotometer at 275.00 nm.

7.3.7 Disintegration time *(Indian Pharmacopoeia, 2007;Chaudhari P.D., 2005)*

Method

The Disintegration time of the tablets was determined as per Indian Pharmacopoeia monograph. The test was carried out using USP disintegrate test apparatus, (Veego scientific VTD-DV). It consists of an apparatus in which 6 tablets was introduced into each of six cylindrical tubes, the lower end of which was covered by a

0.025 in wire mesh. The tubes were then raised and lowered through a distance of 5.3 to 5.7 cm in a test fluid phosphate buffer pH 6.8 and 0.1N HCl pH 1.2 as a disintegrating media maintained at $37^0 \pm 2^0$ C. and the time in second taken for complete disintegrate of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

7.3.8 Wetting time of water absorption Ratio

(*Chaudhari P.D., 2005; Gattani S. G.,2009)*

The wetting time characteristic of the loose disintegrant powder allows an evaluation of both the intrinsic swelling and the wettability of the superdisintegrants. Wetting time of the ODT is important parameter, which needs to be assessed to give an in sight into the disintegrate properties of the tablets; a lower wetting time implies a quicker disintegrate of the tablet. Wetting time was performed at room temperature.

A piece of tissue paper of 10cm folded twice was placed in small petri dish of diameter 10cm containing 6 ml of water. A tablet was put on the paper and the timerequired for water to reach upper surface of tablet was noted.

For water absorption ratio the same wetted tablet was taken out from petri dish and weighed.Water absorption ratio (R) was determined by using following equation.

$$R=100\times W_a- W_b/W_b$$

Where,

W_b =Weight of tablet before water absorption

W_a = Weight of tablet after water absorption

7.3.9 In-vitro Dissolution studies

(Indian Pharmacopoeia, 2007; Gattani S. G.,2009; Kuchekar B.S.,2004)

Method

Dissolution profiles of Loratadine tablets were determined using the USP Type II Dissolution test apparatus (Veego scientific VDA-8DR) set with a paddle speed of 100 rpm. Dissolution was performed in 900 ml of 0.1N HCl maintained at $37^0 \pm 0.5^0$C. Aliquot of dissolution medium, 5 ml was with drawn at 3, 6, 9, up to 12 min with 5minutes interval, and filtered through Whatmann filter paper. The amount of drug dissolved was determined by UV-Visible spectrophotometer **(**Shimadzu-1700 Pharmaspec UV-VIS Spectrophotometer**)** by measuring the absorbance of the sample at 247.5 nm. An equal volume of fresh medium, prewarmed at 37^oC was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. Three trials for each batch were performed and average percentage drug release was calculated by using PCP disso V3 software.

7.4. Stability studies of the tablets *(www.ich.org.com,Chaudhari P.D.,2005)*

Stability of a formulation can be defined as the time from date on manufacture of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. Formulation and the development of a pharmaceutical product are not complete without proper stability analysis, carried out on it to assess the physical and chemical stability and the safety. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time. Under the influence

of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf lives.

Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid the undesirable delay, the principles of accelerated stability studies are adopted.

The International Conference on Harmonization (ICH) Guidelines titled "Stability testing of new drug substance and products" (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and United States of America.

ICH specifies the length of study and storage conditions.

Long-term testing 25^{o} C ± 2^{o} C/60 % RH ± 5% for 12 months.

Short term testing 30^{o} C ± 2^{o} C/65 % RH ± 5% for 1 month.

Accelerated testing 40^{o} C ± 2^{o} C/75 % RH ± 5% for 6 months.

Stability studies for the present work carried out at 40^{o} C ± 2^{o} C/75% ± 5% RH for the selected formulation for 3 months.

Method

The selected formulations were packed in tightly closed container which were tightly plugged with cotton and capped. They were then stored at 40^{o} C ± 2^{o} C /75 % RH ± 5% for 3 months and evaluated for their physical appearance, hardness, disintegrate time, dissolution testing and drug content at specified intervals of time. The drug solutions were further scanned to observe any possible spectral changes.

Results and Discussion

8. RESULTS AND DISCUSSION

In the present study, an attempt was made to formulate nine formulations of the mouth dissolving tablets of Loratadine were prepared with different level addition of superdisintegrants; sodium starch glycollate, crosspovidone and Croscarmellose sodium, For each designed formulations, powder mixed blend of drug and excipients was prepared and evaluated for various parameters as follows.

8.1. Preformulation parameters

8.1.1. Identification of drug

8.1.1.1. By FTIR spectroscopy

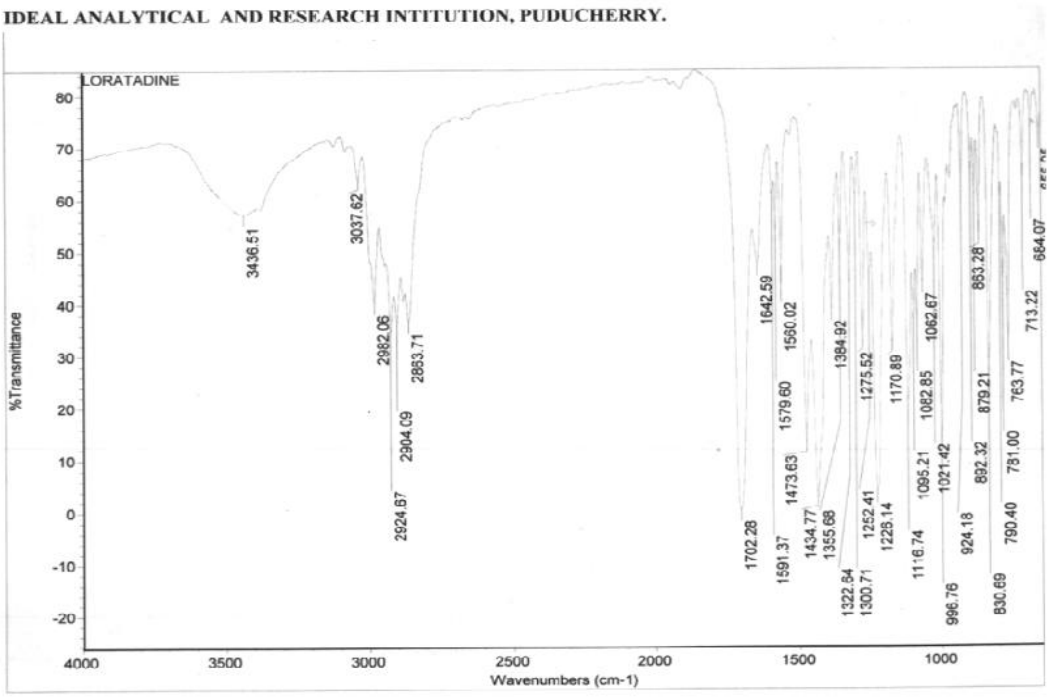


Figure 8.1: FTIR spectra for Loratadine

Table 8.1: Characteristic frequencies (Interpretation) in IR spectrum of Loratadine

Wave No.(cm^{-1})	**Inference**
1702.28	C=O stretching
713.22	C-Cl stretching
3037.27	C-H stretching of pyridine
1591.37	C=N stretching of pyridine
2982.06	C-H stretching of aromatics
1579.60	C-C skeletal stretching
1355.68	C-N stretching of tertiary amine

Major functional groups present in Loratadine show characteristic peaks in IR spectrum. Table 8.1 shows peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to functional group of Loratadine. Hence, the sample was confirmed as Loratadine.

8.1.1.2. By melting points

Melting range of Loratadine sample was found to be **135.00 ± 1^0C**. The reported melting point range for Loratadine is 134 to 136ºC. Hence, experimental values are in good agreement with official values.

8.1.2. Physicochemical parameters of drug

8.1.2.1.Organoleptic properties

Colour: White

Nature: Fine powder

Odour: Odourless

8.1.2.3. Solubility study of the drug

Table 8.2: The solubility of Loratadine in different solvents

S. No.	Solvent	Parts of solvent required per part of solute	Inference
1	Distilled water	1000	Practicallly Insoluble
2	Acetone	2	Freely Soluble
3	Methanol	2	Freely Soluble
4	Chloroform	2	Freely Soluble
5	Toluene	2	Freely Soluble
6	0.1 N HCl	2	Freely Soluble

8.1.4 Loss on drying

The percentage loss on drying after 4 hours was found to be 0.4%. The sample passes test for loss on drying as per the limits specified in I.P.(N.M.T. 0.5%).

Table 8.3: Percentage loss on drying for Loratadine

S. No.	Percentage LOD	Avg. percentage LOD
1	0.3	0.3±0.1
2	0.2	
3	0.4	

8.1.5 Analytical Methods.

8.1.5.1. Determination of λmax. and Preparation of Calibration Curve of Loratadine by using 0.1 N HCl.

UV absorption spectrum of Loratadine in 0.1 N HCl shows λmax at 247.5 nm. Absorbance obtained for various concentrations of Loratadine in 0.1 N HCl are given in table 8.4.The graph of absorbance vs. concentration for Loratadine was found to be linear in the concentration range of 10µg /ml. The drug obeys Beer- Lambert's law in the range of 10 µg /ml.

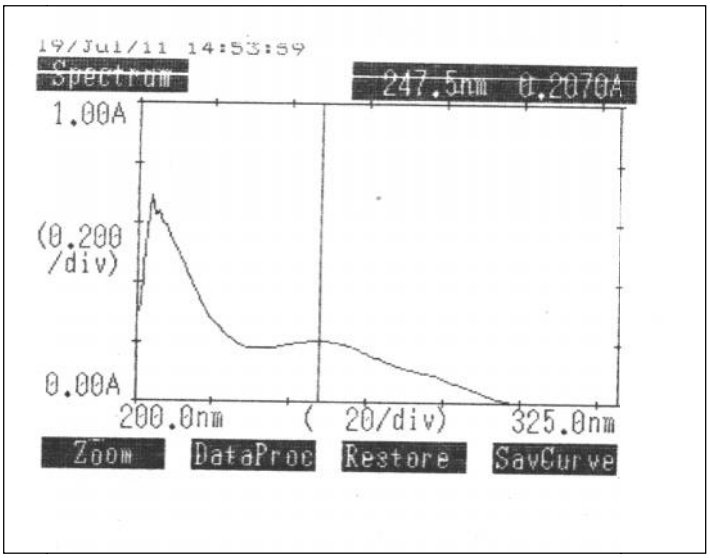


Figure 8.2: UV Spectra of Loratadine in 0.1 N HCl

Table 8.4: Data of Concentration and Absorbance

S. No.	Concentration (µg/ml)	Absorbance at 247.5 nm
1	5	0.186
2	10	0.339
3	15	0.527
4	20	0.663
5	25	0.879
6	30	1.050

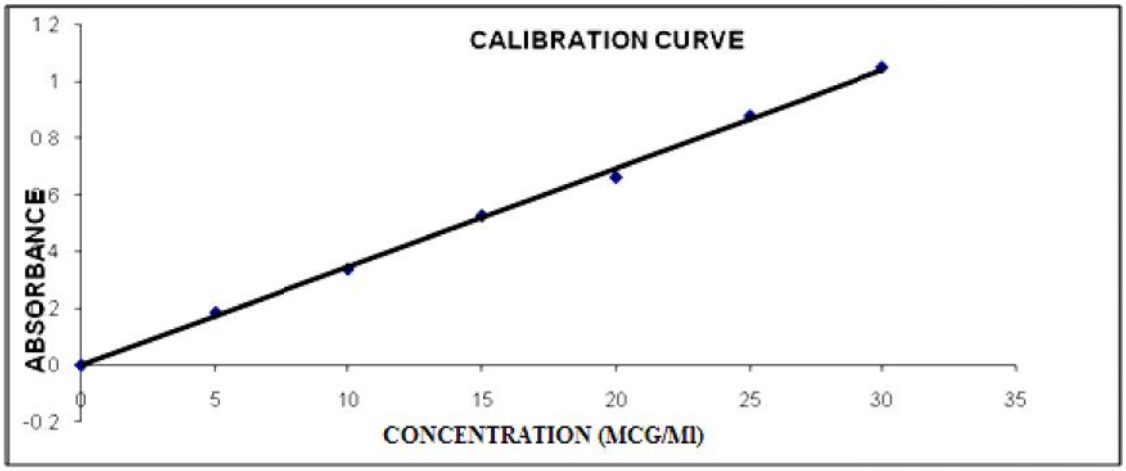


Figure 8.3: Calibration curve for Loratadine in 0.1 N HCl

The values of Correlation coefficient (R), Slope, Intercept obtained from the calibration curve are given in the following table.

Table 8.5: Data for Calibration Curve Parameters

S. No.	Parameters	Values
1	Slope (m)	0.03472
2	Intercept(c)	0.00014
3	Correlation coefficient (R)	0.99915

8.1.5.2 Determination of λ max and Preparation of Calibration Curve of Loratadine by using Methanol

UV absorption spectrum of Loratadine in Methanol shows λmax at 275 nm. Absorbance obtained for various concentrations of Loratadine in Methanol are given in table 8.6. The graph of absorbance vs. concentration for Loratadine was found to be linear in the concentration range of 10µg /ml. The drug obeys Beer Lambert'slaw in the range of 10 µg /ml.

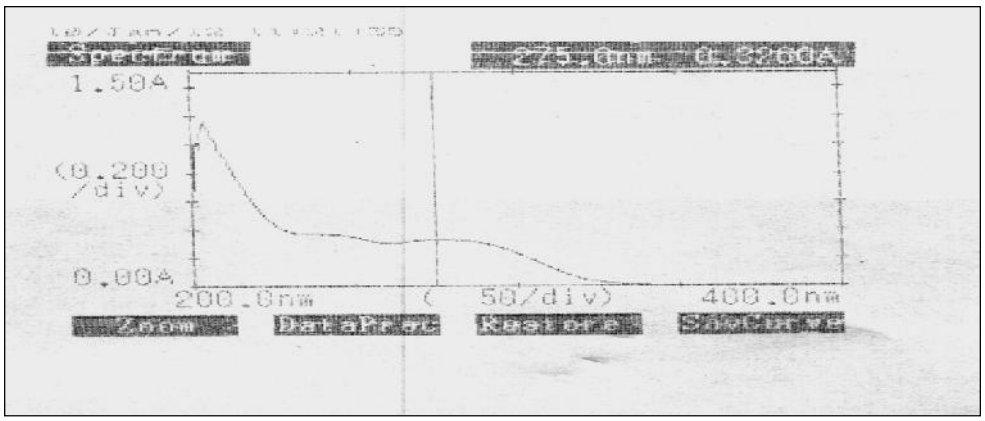


Figure 8.4: UV spectra of Loratadine in Methanol

Table 8.6: Data of concentration and absorbance

S. No.	Concentration (µg/ml)	Absorbance at 275 nm
1	5	0.1623
2	10	0.3256
3	15	0.4894
4	20	0.6543
5	25	0.8143
6	30	0.9768

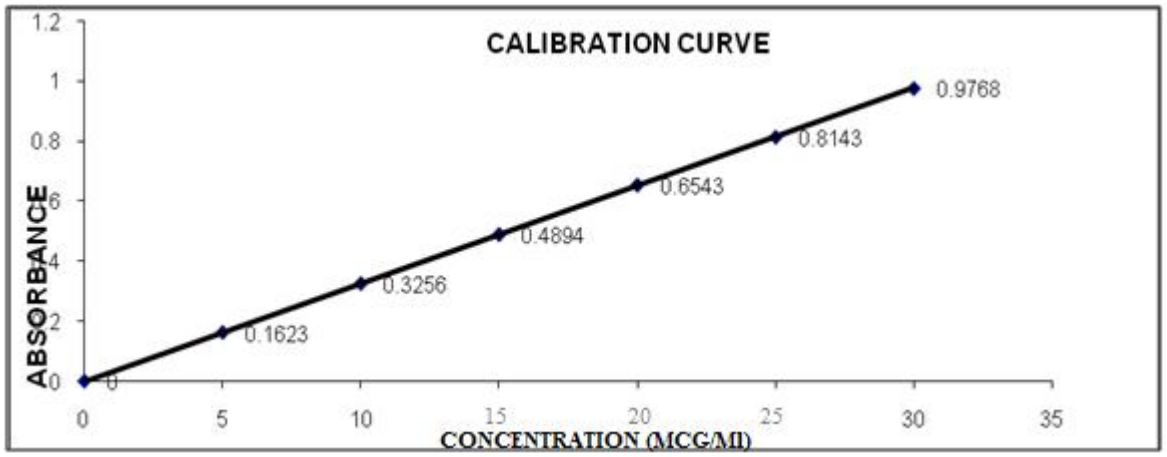


Figure 8.5: Calibration curve for Loratadine in Methanol

Table 8.7: Data for calibration curve parameters

S. No.	Parameters	Values
1	Slope (m)	0.032594
2	Intercept(c)	0.0000536
3	Correlation coefficient (R)	0.9999

8.1.5.3. Determination of λmax and preparation of calibration curve of Loratadine by using phosphate buffer pH 6.8

UV absorption spectrum of Loratadine in phosphate buffer pH 6.8 shows λmax at 274 nm. Absorbance obtained for various concentrations of Loratadine in phosphate buffer pH 6.8 are given in table 8.8. The graph of absorbance Vs concentration for Loratadine was found to be linear in the concentration range of 10µg /ml. The drug obeys Beer- Lambert's law in the range of 10 µg/ml.

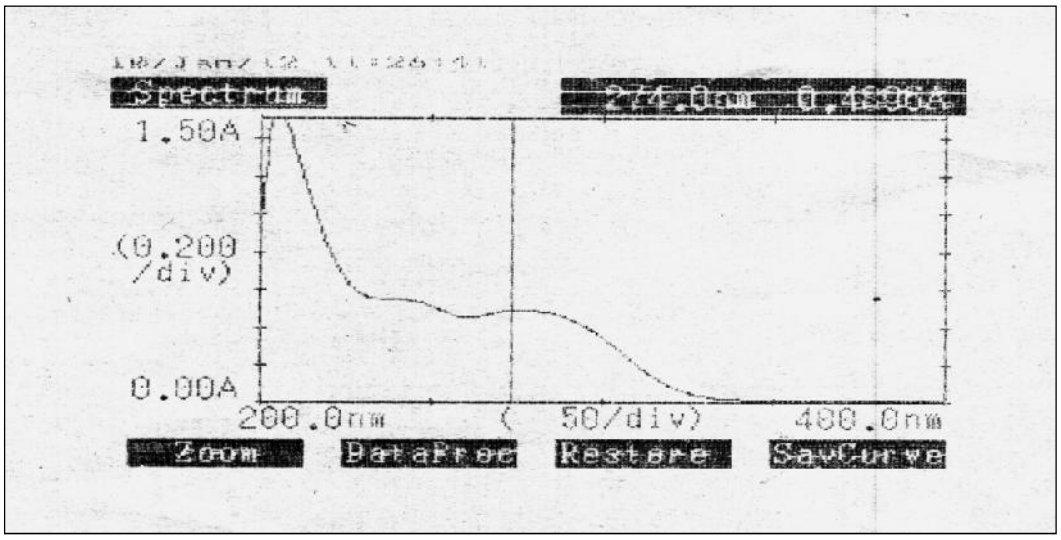


Figure 8.6: UV spectra of Loratadine in Phosphate buffer pH 6.8

Table 8.8: Data of concentration and absorbance.

S. No.	Concentration (µg/ml)	Absorbance at 274 nm
1	5	0.2438
2	10	0.4891
3	15	0.7338
4	20	0.9945
5	25	1.2396
6	30	1.4921

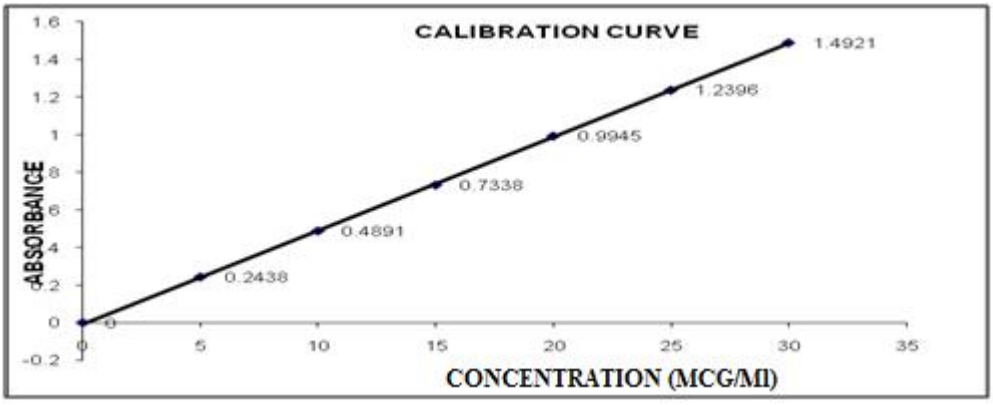


Figure 8.7: Calibration curve for Loratadine in Phosphate buffer pH 6.8

The values of Correlation coefficient (R), Slope, Intercept obtained from the calibration curve are given in the following table.

Table 8.9: Data for calibration curve parameters

S. No.	Parameters	Values
1	Slope (m)	0.049809
2	Intercept(c)	0.0053
3	Correlation coefficient (R)	0.999963

8.1.2.3. Percentage purity of pure drug

The percentage purity of drug was calculated by using calibration graph method (least square method).

Table 8.10: Percentage purity of pure drug

S. No.	Percentage purity (%)	Avg. percentage purity (%)
1	100.98	100.10 ± 0.64
2	99.64	
3	99.58	

All values are expressed as mean± SE, n=3.

The reported percentage purity for Loratadine is 99 to 101% (I.P. 2007).

8.1.6. Fourier Transform Infra-Red Spectroscopy (FT-IR)

Major functional groups present in Loratadine show characteristic peaks in IR spectrum. Table No.8.11 shows peaks observed at different wave numbers and the functional group associated with these peaks.The major peaks are identical to functional group of Loratadine. Hence, the sample was confirmed as Loratadine.

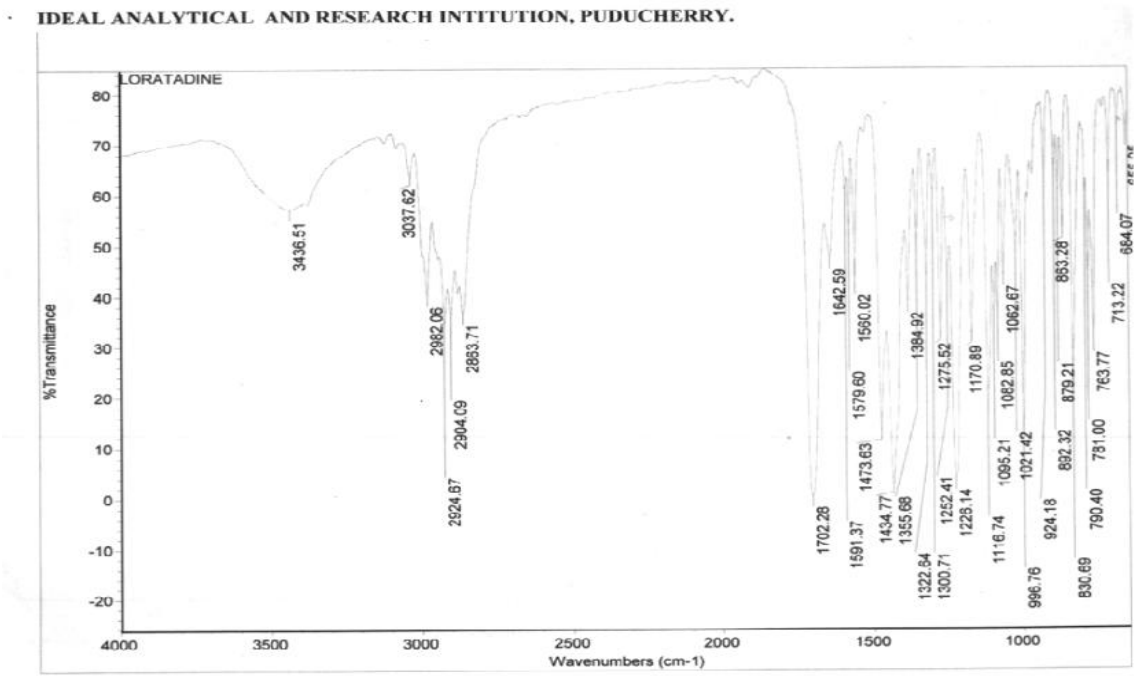


Figure.8.8: FTIR spectrum of Loratadine

8.1.7. Drug and superdisintegrant compatibility studies

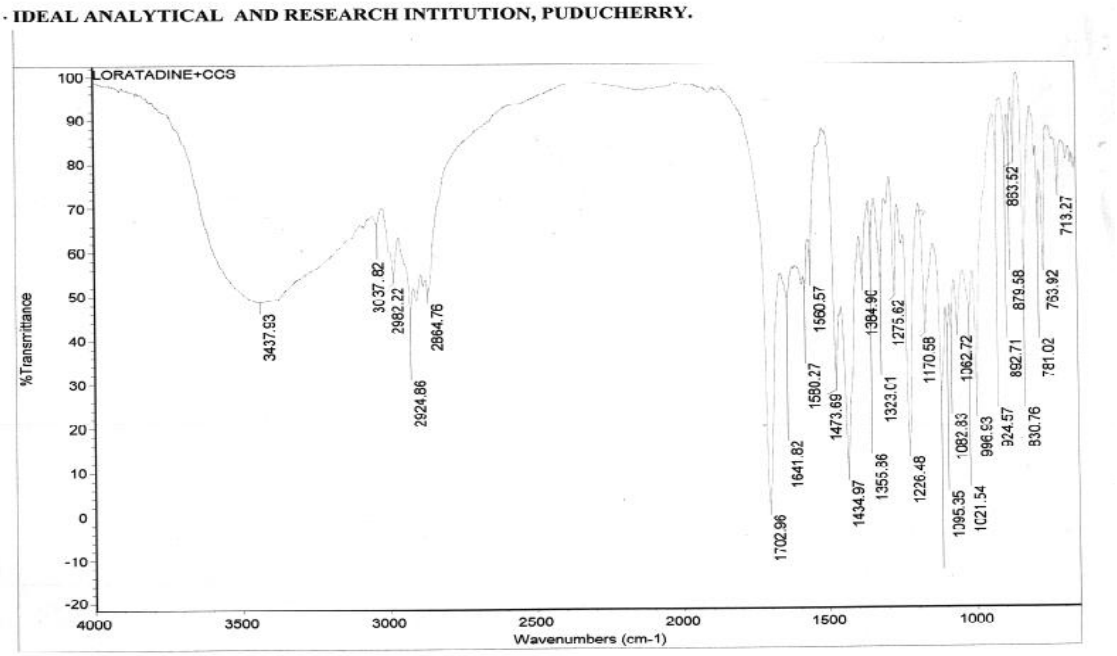


Figure 8.9: FTIR spectra for Loratadine + croscarmellose sodium

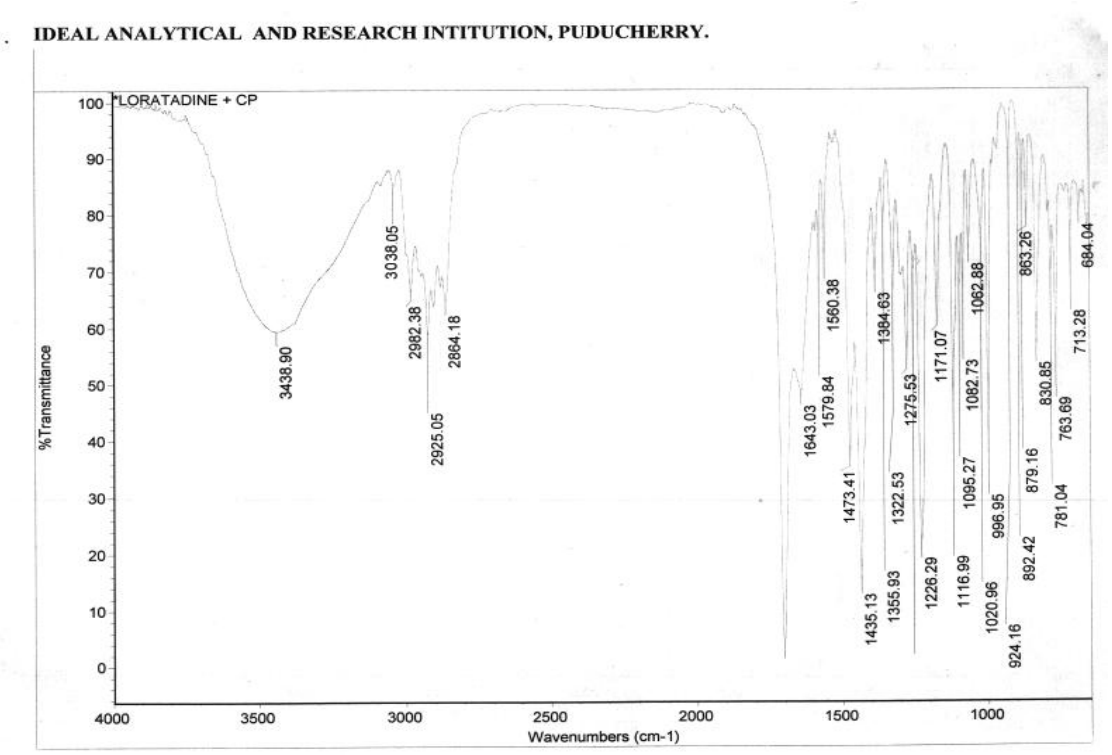


Figure 8.10: FTIR spectra for Loratadine + crospovidone

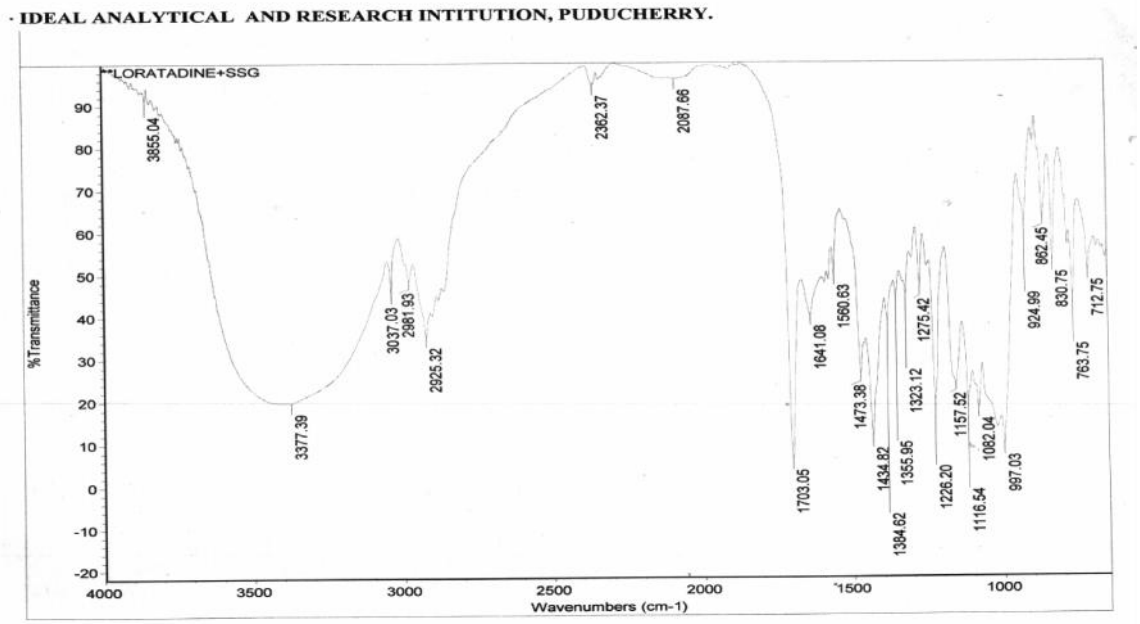


Figure 8.11: FTIR spectra for Loratadine + sodium starch glycolate

Table 8.11: Interpretation of FTIR Spectra of Loratadine

Wave No. (cm^{-1})	**Functional group**	**Peak observed (Yes/No)**			
		Drug	**Drug + CCS**	**Drug +SSG**	**Drug + CP**
1702.28	C=O stretching	**Yes**	**Yes**	**Yes**	**Yes**
713.22	C-CL stretching	**Yes**	**Yes**	**Yes**	**Yes**
3037.62	C-H stretching	**Yes**	**Yes**	**Yes**	**Yes**
1591.37	C-=N stretching	**Yes**	**Yes**	**Yes**	**Yes**
2982.06	C-H stretching	**Yes**	**Yes**	**Yes**	**Yes**
1579.60	C-C skeletal stretching	**Yes**	**Yes**	**Yes**	**Yes**
1355.68	C-N stretching of tertiary amine	**Yes**	**Yes**	**Yes**	**Yes**

SSG =Sodium starch glycollate, CP= Crospovidone, CCS = Croscarmellose sodium

Observation

Drug-excipient mixture does not produce any significant changes in organoleptic property, bulk density, true density, compressibility index, angle of repose and drug content. The compatibility between the drug and the selected superdisintegrants were evaluated using FTIR peak matching method.

From above interpretation table it was concluded that, there was no appearance or disappearance of the Principal peaks in the superdisintegrants drug mixture, which confirmed the absence of any chemical incompatibility between the drug and the superdisintegrants.

8.1.7.Differential scanning calorimetry:

The compatibility and interactions between drug and polymer were checked using differential scanning calorimetry results obtained were shown in Figures: 8.12, 8.13, 8.14, and 8.15. Table 8.11

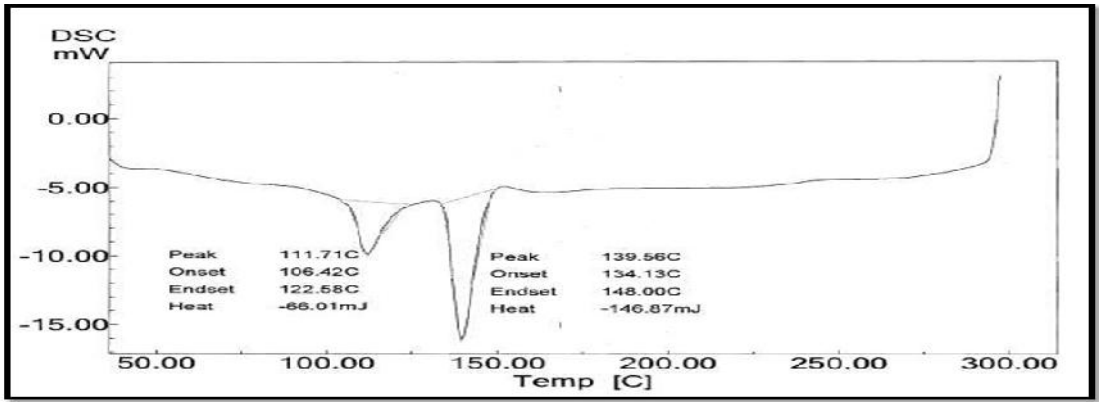


Figure 8.12: DSC of Loratidine

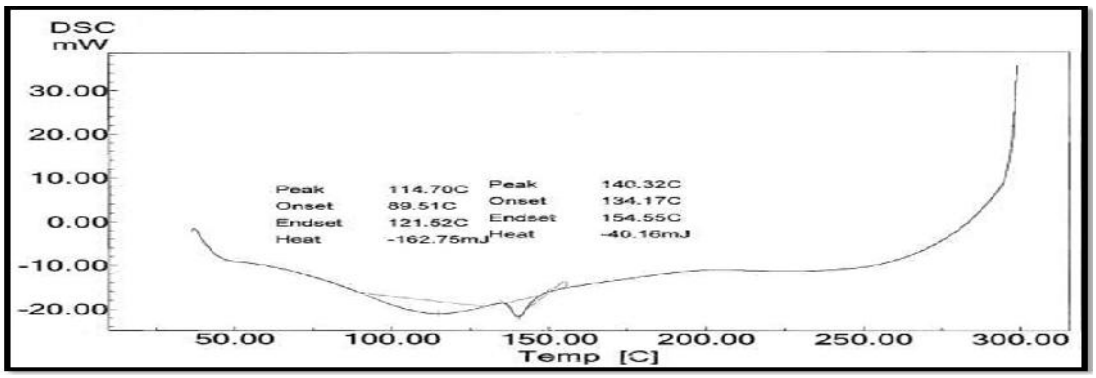


Figure 8.13: DSC of Loratidine + Croscarmellose sodium

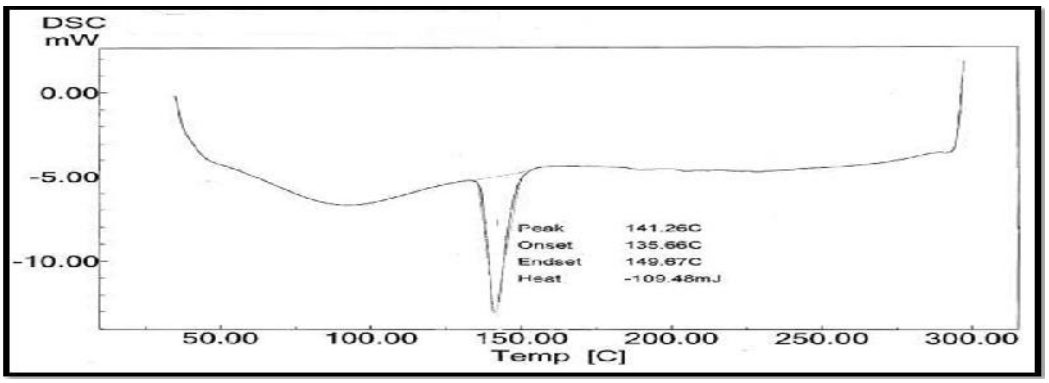


Figure 8.14: DSC of Loratidine + Sodium starch glycolate

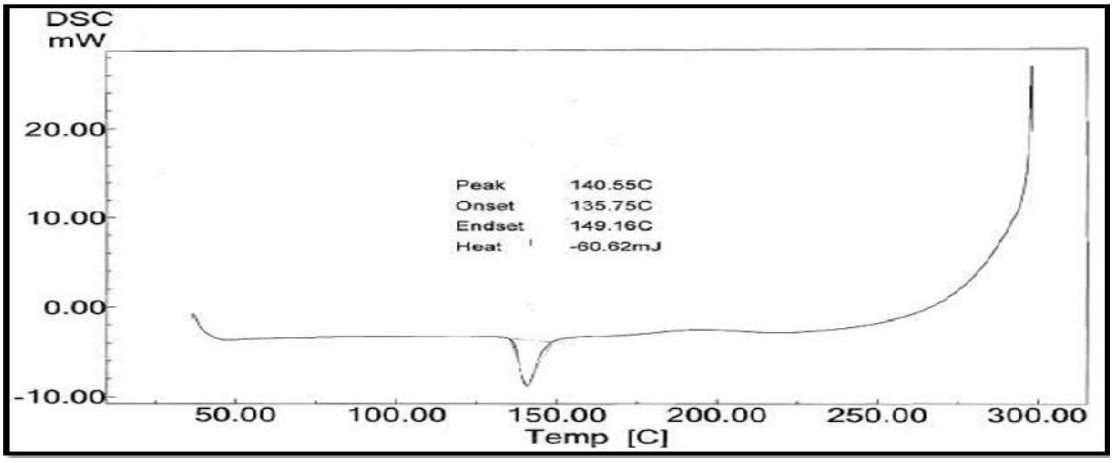


Figure 8.15: DSC of Loratidine + Crospovidone

According to Figures 8.12 to 8.15 and Table 8.12, DSC thermogram showed that there was no major difference in onset temperature, end set temperature and peak temperature when compared with pure drug thermogram. Therefore it could indicate that there was no incompatibility between drug and different polymers.

Table 8.12: DSC thermogram parameters of Loratadine with various polymers

S. No.	DSC thermogram	Onset temperature (°C)	Peak temperature (°C)	End set temperature (°C)
1	Loratadine	134.13	139.56	148.00
2	Loratadine + CCS	134.17	140.32	154.55
3	Loratadine+ SSG	135.66	141.26	149.67
4	Loratadine + CP	135.75	140.55	149.16

8.2. Evaluation Of Powder Blends Of Loratadine

Table 8.13: Evaluation of Powder Blends of Loratadine

Formulation Code	Bulk density(g/ml)	Tapped density(g/ml)	Angle of repose(Ɵ)	Carr's index(%)	Hausner's ratio
F1	0.45±0.0125	0.50±0.0231	31.78±1.8815	11.19±0.00	0.8880±0.00
F2	0.43±0.0165	0.49±0.0099	30.67±0.9514	11.45±0.00	0.8854±0.00
F3	0.45±0.0042	0.50±0.0063	34.53±1.7870	9.56±0.00	0.9043±0.00
F4	0.41±0.0105	0.47±0.0124	28.42±1.2725	12.26±0.00	0.8773±0.00
F5	0.45±0.0090	0.52±0.0213	33.78±1.4577	13.79±0.00	0.8620±0.00
F6	0.47±0.0120	0.54±0.0217	29.04±1.1461	12.69±0.00	0.8730±0.00
F7	0.46±0.0103	0.50±0.0107	33.65±0.5445	9.65±0.00	0.9034±0.00
F8	0.48±0.0134	0.56±0.0216	28.66±1.673	14.18±0.00	0.8581±0.00
F9	0.43±0.0171	0.48±0.0263	26.59±0.4705	10.31±0.00	0.8968±0.00

All values are expressed as mean± SE, n=3.

8.2.1. Angle of Repose:

The Angle of repose of various powder mixed blends, prepared with different superdisintegrants, was measured by funnel method.Angle of repose was found in the range **26.59 ± 0.4705 - 34.53^0 ± 1.7870.** The good flow ability of powder blend was also evidence with angle of repose.

8.2.3. Bulk density

The bulk density of various powder mixed blends prepared with different superdisintegrants was measured by graduated cylinder. The bulk density was found in the range **0.41 ± 0.0105 - 0.48 ± 0.0134 g/ml**

8.2.4. Tapped Density

The Tapped density of various powder mixed blends prepared with different superdisintegrants was measured by using measuring cylinder.The tapped density was found in the range **0.47 ± 0.0124 - 0.56 ± 0.0216 g/ml.**These values indicate good packing characteristics and the powder was not bulky.

8.2.5. Compressibility Index

The Compressibility index of various powder mixed blends, prepared with different superdisintegrants, using bulk density and tappeddensity data, compressibility index was calculated. It was found in the range **9.56 ± 0.00 - 14.18± 0.00 %.** This indicates good flow properties.

8.2.6. Hausner's ratio

The Hausner's ratio of various powder mixed blends, prepared with different superdisintegrants, it is calculated by using bulk density and tapped density data. It was found in the range of **0.8581 ± 0.00 – 0.9043 ± 0.00**, reveals good flow properties(<1.25)

8.3. Evaluation of Loratadine Tablets

Table 8.14: Evaluation of Loratadine tablets.

Formulation Code	Dimension		Hardness (kg/cm^2)	Friability (%)	Drug content (%w/w)	Weight variation
	Thickness (mm)	Diameter (mm)				
F1	2.90±0.10	7.86±0.20	3.26± 0.05	0.8±0.05	98.50±0.11	204.6± 1.18
F2	2.9±0.17	7.73±0.32	3.36± 0.11	0.8±0.15	98.75±0.01	205.15 ± 1.59
F3	2.76±0.25	7.83±0.24	3.26± 0.15	0.9±0.1	98.25±0.15	206.15 ± 1.63
F4	2.80±0.10	7.96±0.20	3.36± 0.15	0.9±0.13	95.25±0.13	207.15 ± 1,53
F5	2.70±0.17	7.76±0.32	3.33± 0.25	0.8±0.07	98.50±0.06	207.10 ± 1.61
F6	3.0±0.10	7.80±0.45	3.4± 0.10	0.8±0.09	97.70±0.23	205.10 ± 1.48
F7	2.86±0.11	7.93±0.35	3.4± 0.10	0.8±0.06	97.75±0.14	206.40 ± 1.66
F8	2.96±0.05	7.76±0.30	3.4± 0.10	0.9±0.10	98.75±0.17	207.15 ± 1.53
F9	2.8±0.10	7.83±0.20	3.0± 0.10	0.9±0.11	98.75±0.01	201.55 ± 1.63

All values are expressed as mean± SE, n=3.

8.3.1. Dimension (Thickness and Diameter):

Tablets were evaluated by using Vernier caliper. Excessive variation in the tablet thickness and diameter can result in problems with packaging as well as consumer acceptance. There were no marked variations in the thickness and diameter of tablets within each formulation indicating uniform die fill throughout the compression process.

The size (diameter) of the tablets of all formulations was found to be **7.73 ± 0.3214 – 7.96 ± 0.2081 mm** and thickness ofthe tablets was found in the range of **2.70 ± 0.17 mm – 3.0 ± 0.10 mm**.

8.3.2. Weight variation

Tablets were prepared using direct compression technique. Since the material was free flowing, tablets were obtained of uniform weight due to uniform die fill. Tablets were obtained in the range with acceptable weight variations as per Pharmacopoeia specifications, less than 7.5.

8.3.3.Hardness

Tablets were evaluated by using Monsanto Hardness tester. Hardness of the tablets was in the range **3.0 ± 0.1 - 3.4 ± 0.1 kg/cm^2**. Uniform hardness was obtained due to equal compression force. The obtained hardness range showed good mechanical strength with an ability to withstand physical and mechanical stress conditions.

8.3.4. Friability

Tablets were evaluated by using Roche Friabilator and friability of tablets was observed in acceptable range. **0.8 ± 0.090 - 0.9 ± 0.117** (less than 1%) This indicated a good mechanical resistance of the prepared mouth dissolving tablets.

8.3.5. Drug content of Loratadine

Tablets were evaluated by using assay method. The drug content was obtained in the acceptable limit. The drug content was found in therange **95.25 ± 0.13 - 98.75 ± 0.01 %w/w.** (i.e. 99-101% w/w). The found range was within the specified limit as per Indian Pharmacopoeia 2007.

8.3.6. Disintegration time

Tablets were subjected for the *in-vitro* disintegrate time in the USP Disintegrate test apparatus.(Veego scientific VTD-DV) The *in-vitro* disintegrate time for all nine formulations varied from **12 ± 1.8973 to 30 ± 1.8973 seconds.** The rapid disintegrate was seen in the formulations containing Crospovidone and Croscarmellose sodium. This is due to rapid intake of the water from the medium, swelling and burst effect. It also noticed that the concentration of Croscarmellose sodium followed by Crospovidone and Sodium starch glycollate increased, the time taken for the disintegrate was reduced.

Figure 8.16. Reveals that the formulations with highest concentration of Croscarmellose sodium with Crospovidone shown significant rapid disintegrate.

Disintegrate time was to be found very less for F9 formulation which contains highest concentration and efficiency of Crosspovidone

Figure 8.16: Disintegration of tablet

Table 8.15: Disintegration time in seconds

Formulations	Disintegrate time (sec) (Mean ± S.D. n = 3)
F1	25±3.2863
F2	19±1.4142
F3	15±1.4142
F4	30±1.8973
F5	22±1.4142
F6	18±1.4142
F7	20±2.000
F8	15±1.4142
F9	12±1.8973

All values are expressed as mean± SE, n=3.

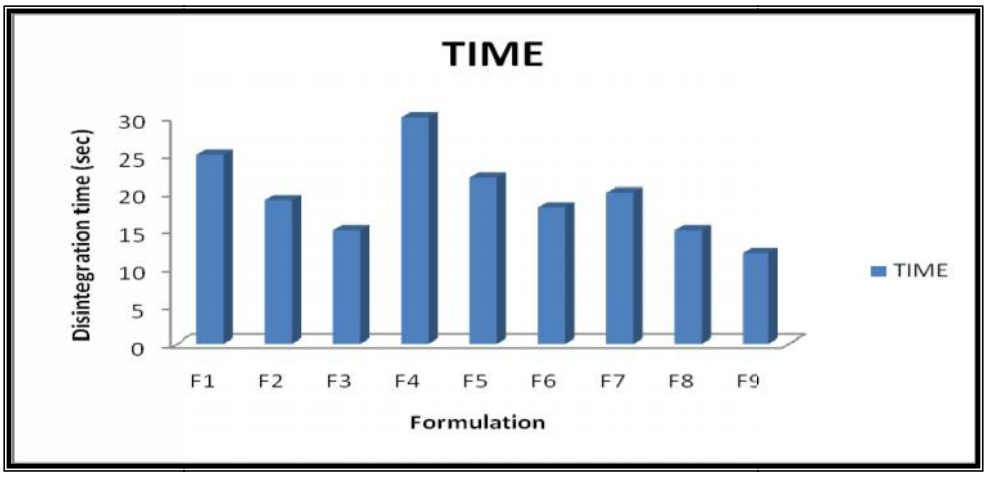


Figure 8.17: Disintegrate profile of mouthdissolving Loratadine tablets (F1 - F9)

8.3.7. Wetting time and water absorption ratio

The wetting time for all nine formulations was performed in duplicate. The values lie between **11 ± 1.4142 to 42 ± 1.8973 seconds.** The wetting time was rapid in Crosscarmellose sodium followed by Crosspovidone and Sodium starch glycollate. Here

also it was observed that as the concentration of disintegrant increased the time taken for wetting was reduced.

Water absorption ratio which is important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water was calculated. It was found in the range of **78.45 ± 5.92 to 125.80 ± 5.10 %.** (table 8.16) Water absorption ratio (R) increases with the increased concentration of Croscarmellose sodium followed by crosspovidone and sodium starch glycollate. Hence Crospovidone had shown highest water absorption **125.80 %** of **F9** and in turn rapid bursting of the same formulations.

Table 8.16: Wetting time and Water absorption ratio

Formulation	Wetting time(sec)	Water absorption ratio (%)
F1	25±3.2863	81.26±0.9832
F2	20±2.0000	90.28±3.982
F3	17±1.4142	117.40±1.88
F4	42±1.8973	78.45±5.92
F5	31±1.4142	84.44±2.96
F6	23±2.2803	96.66±1.41
F7	26±2.0000	84.24±6.02
F8	17±1.4142	96.66±5.40
F9	11±1.4142	125.80±5.10

*All values are expressed as mean± SE, n=3.

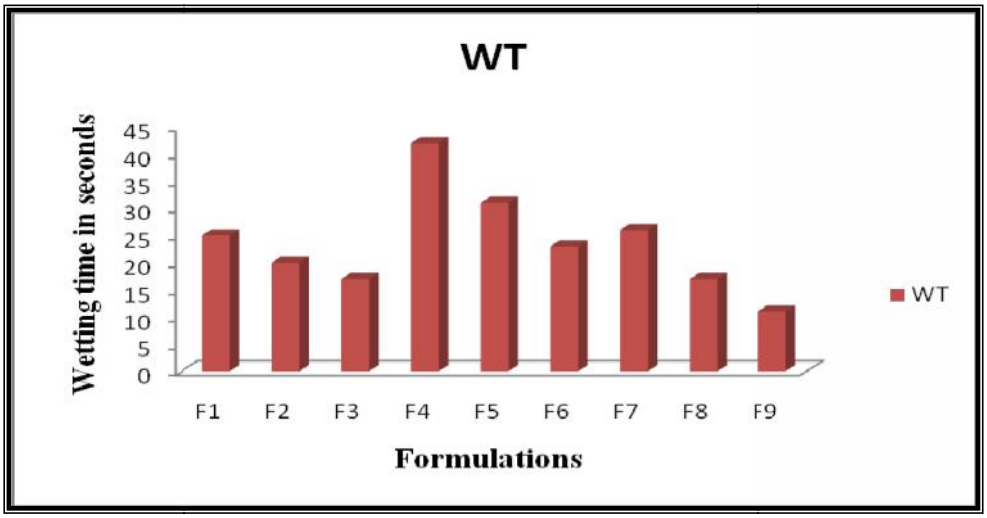


Figure 8.18: Wetting profile of mouth dissolving Loratadine tablets

(F1 - F9)

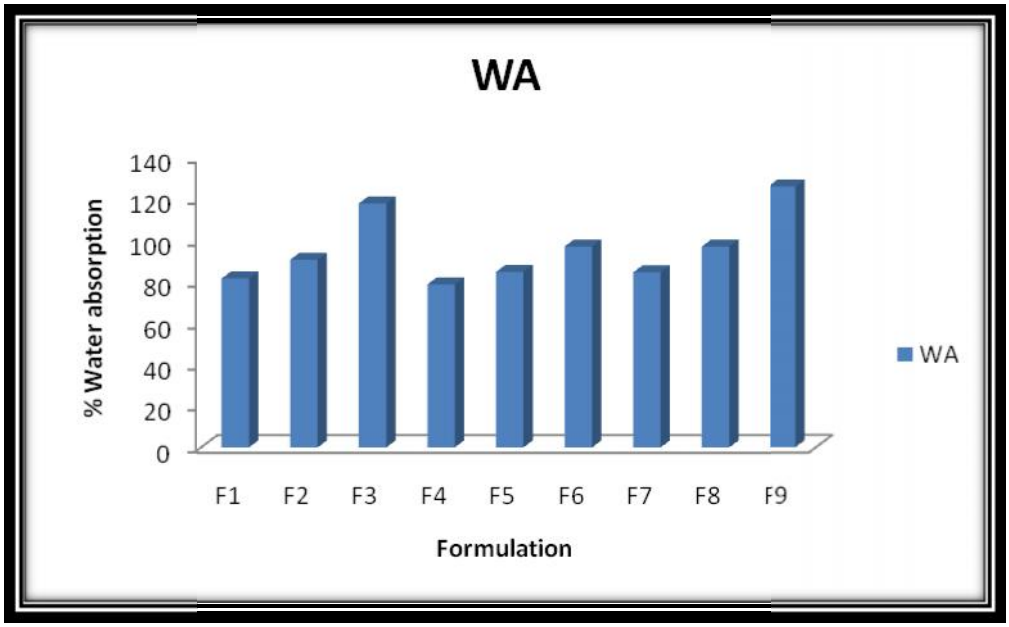


Figure 8.19: Water absorption ratio of mouth dissolving Loratadine tablets

(F1 - F9)

8.3.8. *In –Vitro* Dissolution Studies

Dissolution profile of mouthdissolving Loratadine tablet

Table 8.17: *In-vitro* dissolution data of formulation F1

S. No.	Time (minutes)	Amount of drug released (mg)	%DE	MDT (minutes)	Cumulative % drug Release
1	0	0.00	0.00	0.00	0 ± 0.00
2	3	7.28	36.04	1.50	72.91±0.6266
3	6	7.64	55.24	1.69	76.42 ± 0.7985
4	9	8.54	63.84	2.26	85.5 ± 0.6221
5	12	8.81	69.60	2.57	88.14 ± 0.2214

All the values are expressed as a mean ± SD., n = 3

MDT=Mean dissolution time; % DE= Percent dissolution efficiency

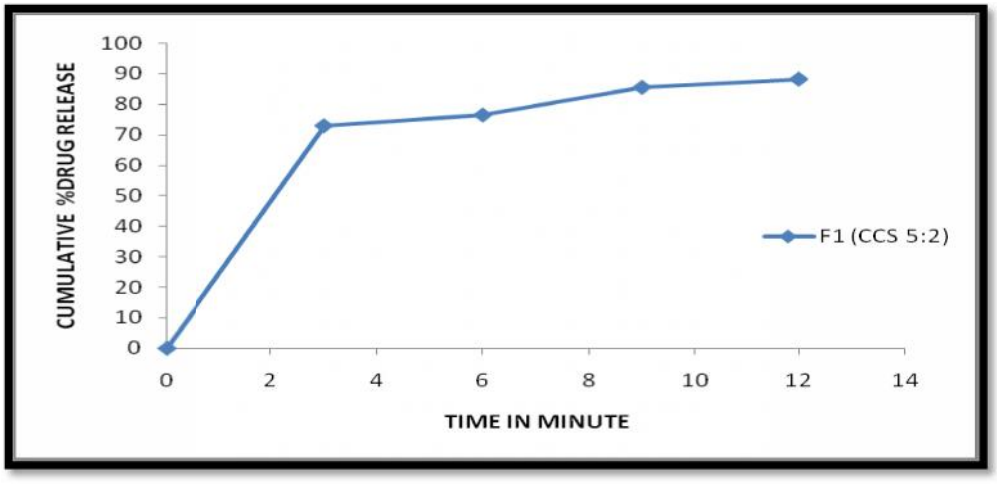


Figure 8.20: Cumulative % drug release profile of formulation F1

Dissolution profile for formulation F2

Table 8.18: *In-vitro* dissolution data of formulation F2

S. No.	Time (Minute)	Amount of drug released (mg)	%DE	MDT (Minute)	Cumulative % drug Release
1	0	0.00	0.00	0.00	0.00
2	3	7.63	37.96	1.50	76.34 ± 0.98
3	6	8.06	58.12	1.68	80.88 ± 0.94
4	9	8.78	66.72	2.11	87.34 ± 0.854
5	12	9.23	72.32	2.51	91.79 ± 1.097

All the values are expressed as a mean ± SD., n = 3

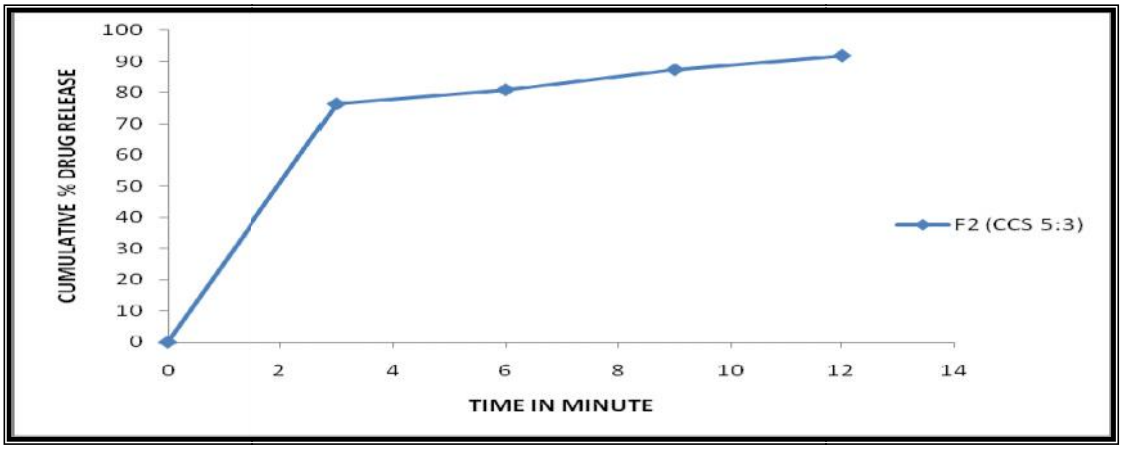


Figure 8.21: Cumulative % drug release profile of formulation F2

Dissolution Profile for Formulation F3

Table 8.19: *In-vitro* dissolution data of Formulation F3

S. No.	Time (Minute)	Amount of drug released (mg)	%DE	MDT (Minute)	Cumulative % drug Release
1	0	0.00	0.00	0.00	0.00
2	3	23.48	39.00	1.33	78.31 ± 1.0102
3	6	25.14	41.21	1.42	83.81 ± 0.9072
4	9	8.99	44.06	1.53	90.01 ± 1.7596
5	12	9.35	45.61	1.58	93.54 ± 0.9073

All the values are expressed as a mean ± SD., n = 3

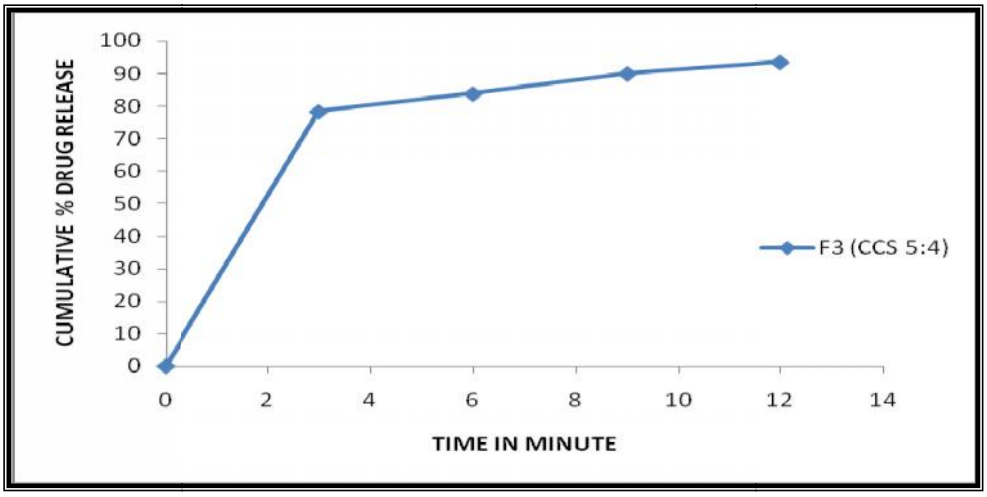


Figure 8.22: Cumulative % drug release profile of formulation F3

Dissolution Profile for formulation F4

Table 8.20: *In-vitro* dissolution data of formulation F4

S. No.	Time (minute)	Amount of drug released (mg)	%DE	MDT (Minute)	Cumulative % drug Release
1	0	0.00	0.00	0.00	0.000 ± 0.00
2	3	7.01	35.07	1.50	70.20± 1.9053
3	6	8.22	53.80	1.69	74.05± 0.5212
4	9	8.9	61.71	2.07	80.16 ± 1.0627
5	12	9.48	66.95	2.57	85.43 ± 0.5692

All the values are expressed as a mean ± SD., n = 3

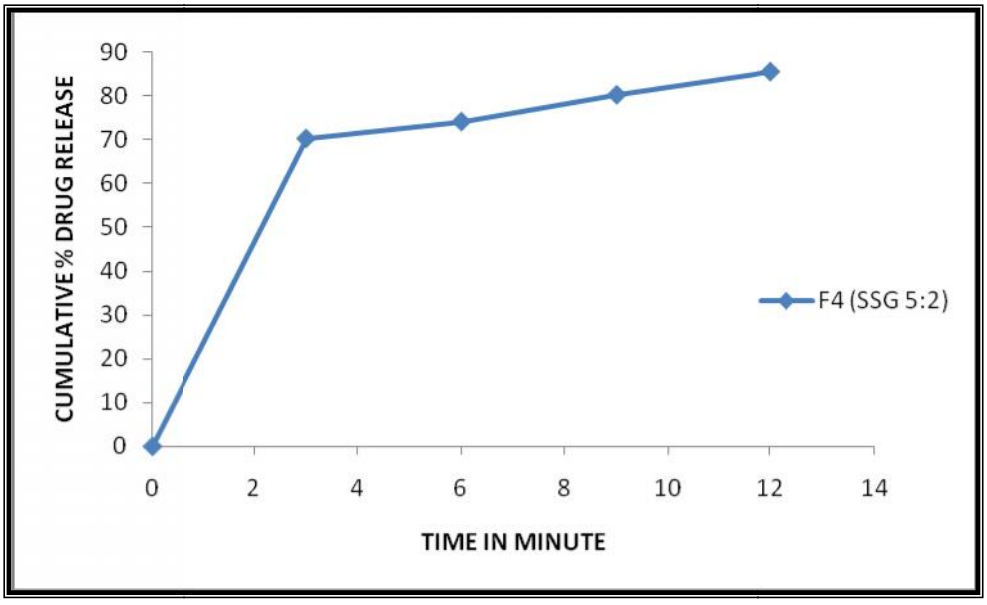


Figure 8.23: Cumulative % drug release profile of formulation F4

Dissolution Profile for Formulation F5

Table 8.21: *In-vitro* dissolution data of Formulation F5

S. No.	Time (Minute)	Amount of drug released (mg)	%DE	MDT (Minute)	Cumulative % drug Release
1	0	0.00	0.00	0.00	0.00
2	3	7.25	36.34	1.50	72.58 ± 0.4653
3	6	7.93	56.11	1.74	79.36 ± 1.5224
4	9	8.32	64.56	2.07	83.30 ± 2.9131
5	12	8.78	69.86	2.45	87.89 ± 1.3618

All the values are expressed as a mean ± SD., n = 3

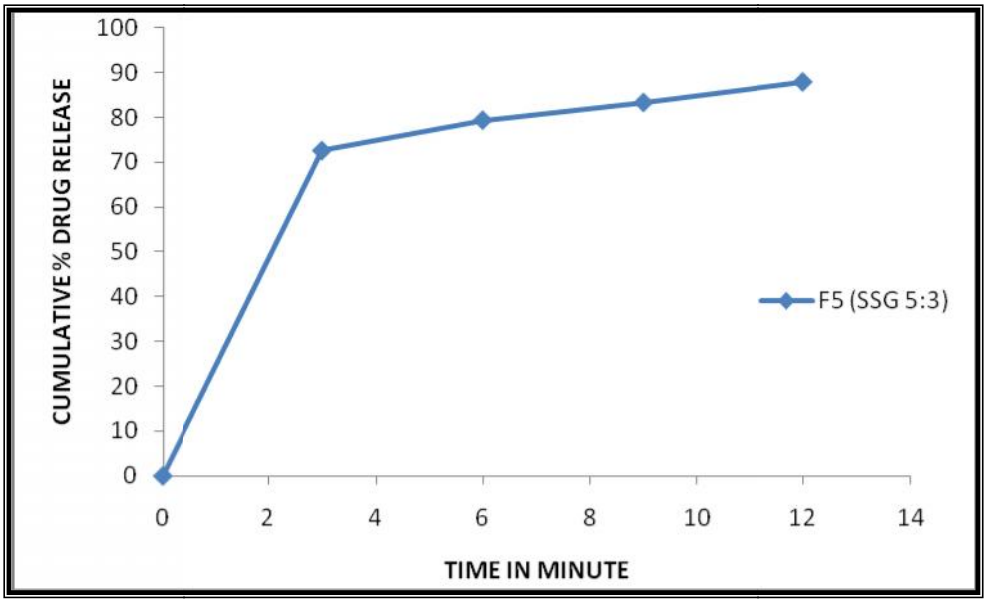


Figure 8.24: Cumulative % drug release profile of formulation F5

Dissolution profile for formulation F6

Table 8.22: *In vitro* dissolution data of formulation F6

S. No.	Time (Minute)	Amount of drug released (mg)	%DE	MDT (Minute)	Cumulative % drug Release
1	0	0.00	0.00	0.00	0.00
2	3	7.60	38.15	1.50	76.13 ± 0.9595
3	6	8.09	58.30	1.66	80.97 ± 1.3054
4	9	8.74	66.83	2.10	87.52 ± 0.5105
5	12	9.09	72.38	2.44	90.96 ± 0.6814

All the values are expressed as a mean ± SD., n = 3

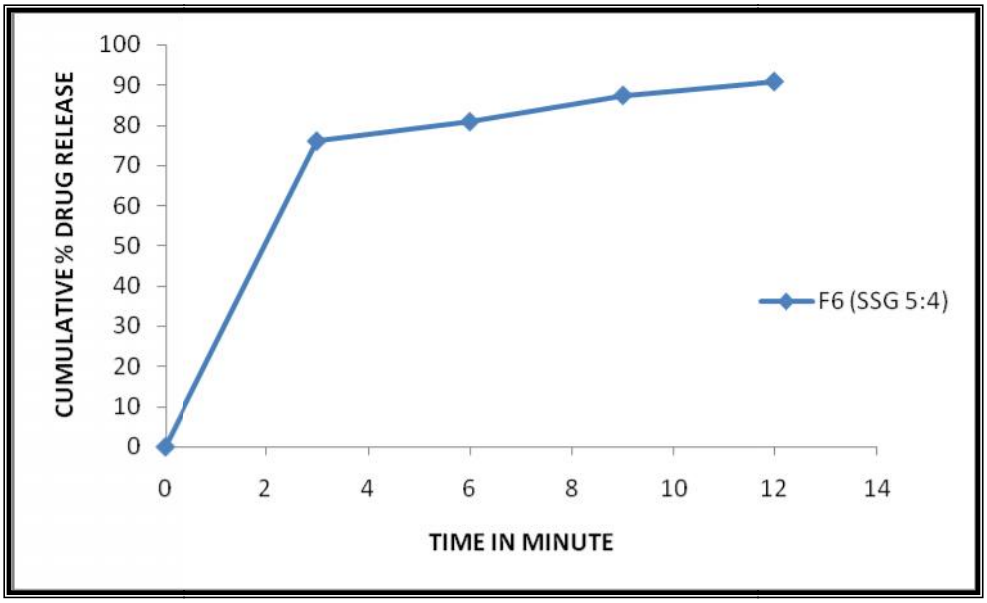


Figure 8.25: Cumulative % drug release profile of formulation F6

Dissolution profile for Formulation F7

Table 8.23: *In-vitro* dissolution data of Formulation F7

S. No.	Time (Minute)	Amount of drug released (mg)	%DE	MDT (Minute)	Cumulative % drug Release
1	0	0.00	0.00	0.00	0.00 ± 0.00
2	3	7.60	38.18	1.50	76.07 ± 0.3220
3	6	8.11	58.46	1.68	81.24 ± 0.9209
4	9	8.70	67.04	2.09	87.09 ± 0.1330
5	12	9.19	72.63	2.47	91.92 ± 0.6291

All the values are expressed as a mean ± SD., n = 3

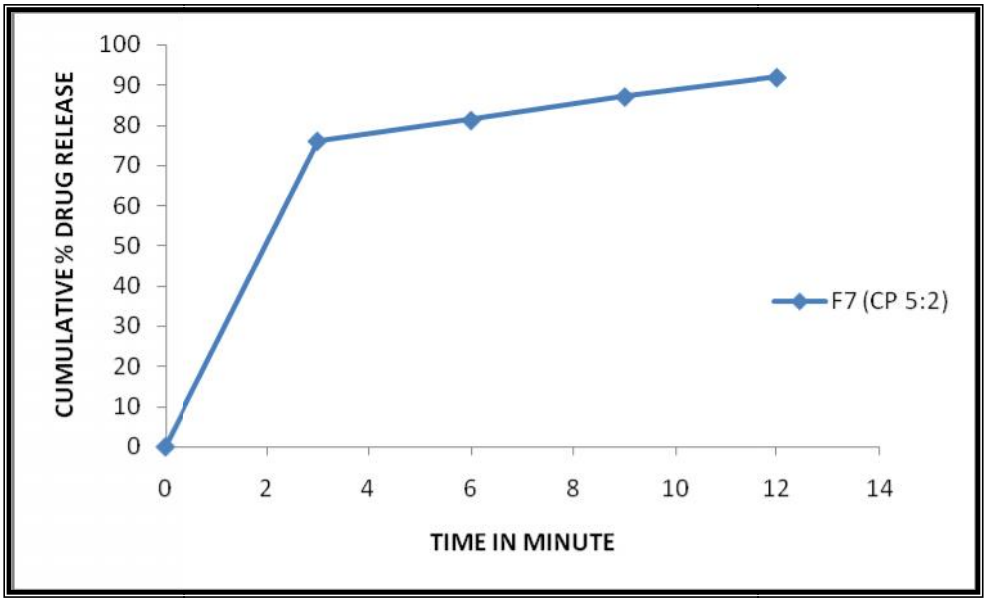


Figure 8.26: Cumulative % Drug release profile of formulation F7

Dissolution profile for Formulation F8

Table 8.24: *In-vitro* dissolution data of Formulation F8

S. No.	Time (Minute)	Amount of drug released (mg)	%DE	MDT (Minute)	Cumulative % drug Release
1	0	0.00	0.00	0.00	0.00 ± 0.00
2	3	8.10	40.61	1.50	81.11 ± 1.0369
3	6	8.51	62.65	1.66	85.20 ± 0.8182
4	9	9.01	70.71	1.95	90.13 ± 2.2305
5	12	9.61	76.40	2.51	96.17 ± 2.112

All the values are expressed as a mean ± SD., n = 3

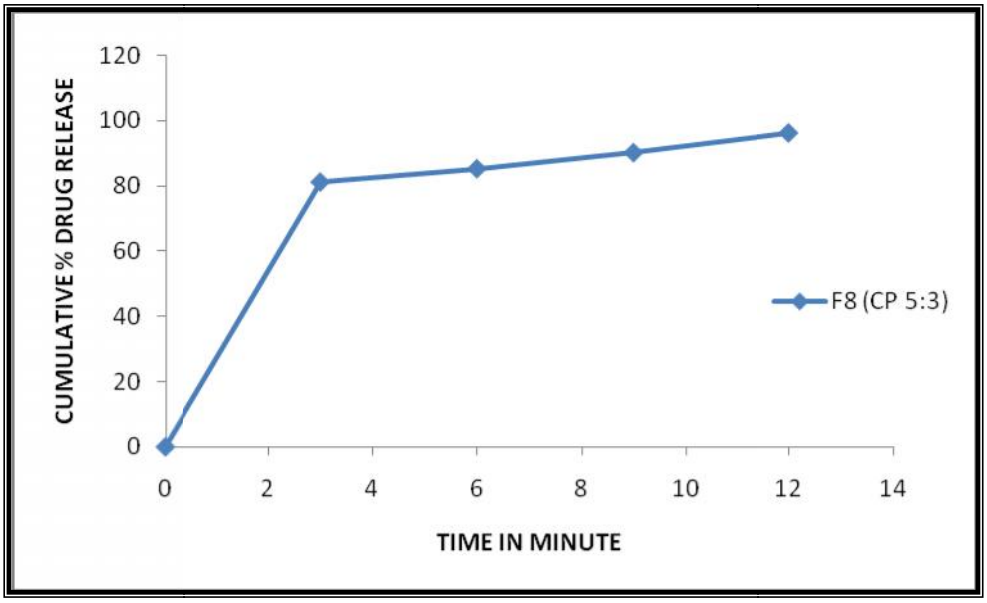


Figure 8.27: Cumulative % Drug release profile of formulation F8

Dissolution Profile for formulation F9

Table 8.25: *In-vitro* dissolution data of formulation F9

S. No.	Time (Minute)	Amount of drug released (mg)	%DE	MDT (Minute)	Cumulative % drug Release
1	0	0.00	0.00	0.00	0.00 ± 0.00
2	3	9.49	42.92	1.50	85.42 ± 1.6733
3	6	9.17	65.79	1.68	91.78 ± 0.9055
4	9	9.69	75.33	2.04	96.40 ± 1.5832
5	12	9.90	81.12	2.23	99.10 ± 0.9422

All the values are expressed as a mean ± SD., n = 3

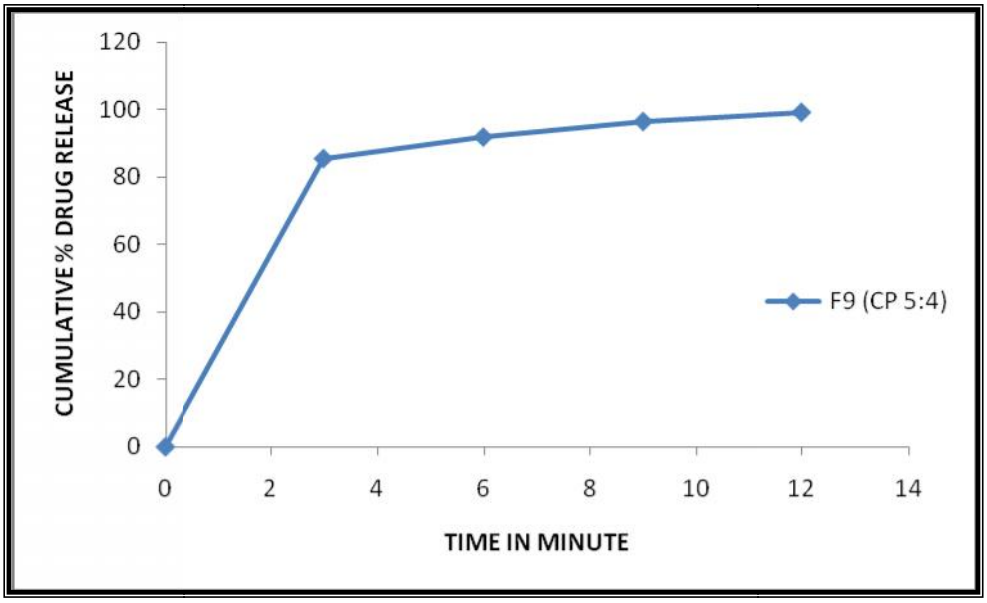


Figure 8.28: Cumulative % drug release profile of formulation F9

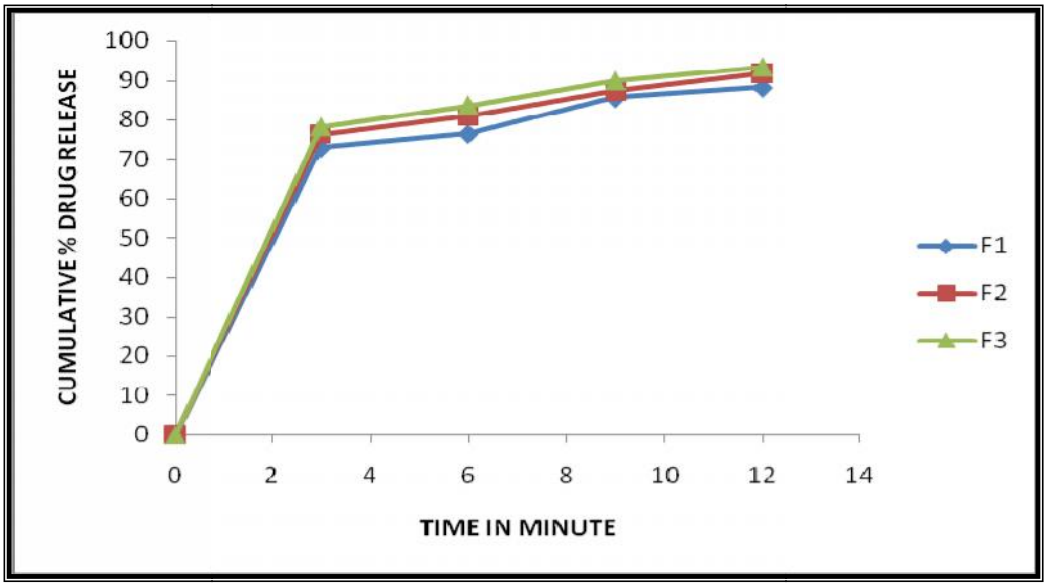


Figure 8.29: Cumulative % drug release profile of formulation F1 – F3

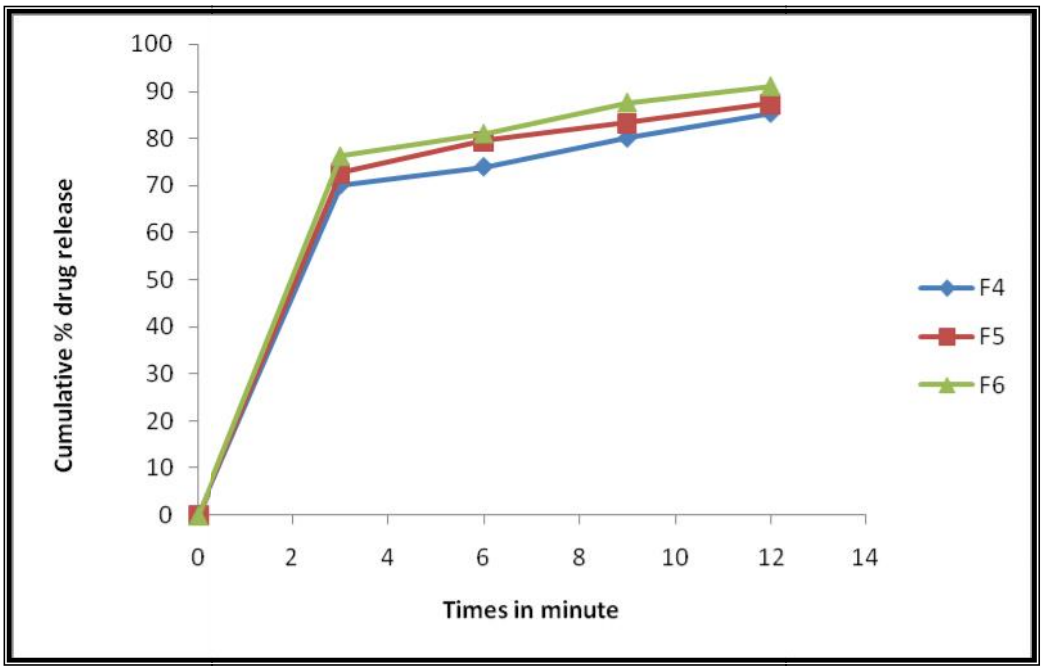


Figure 8.30: Cumulative % drug release profile of formulation F4 – F6

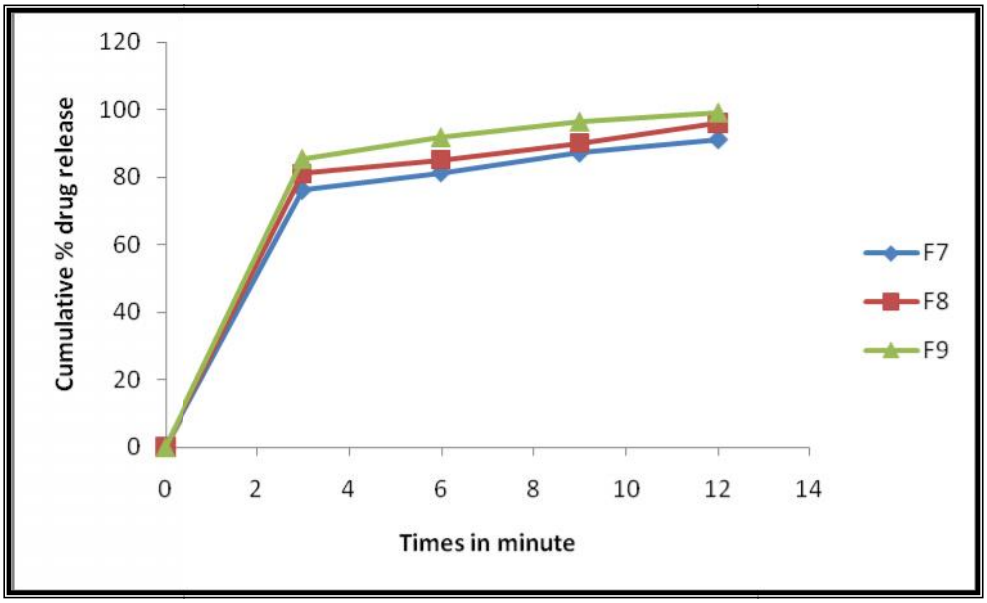


Figure 8.31: Cumulative % drug release profile of formulation F7 – F9

Dissolution Profile of Mouth Dissolving Loratadine Tablets (F1 - F9)

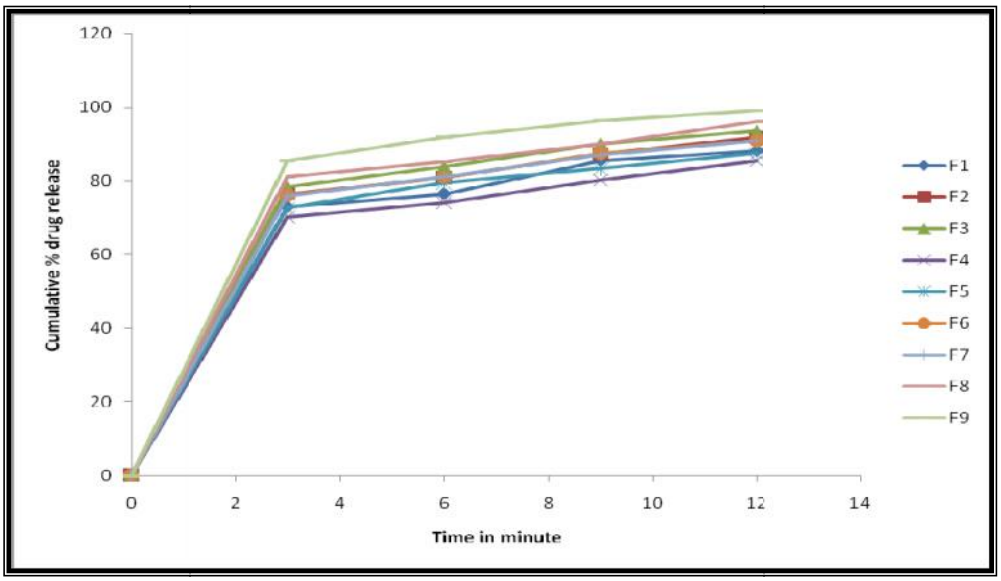


Figure 8.32: Cumulative % drug release profile of formulation F1 – F9

8.4. STABILITY STUDIES

8.4.1 Ageing studies for optimized formulation F9 of mouth dissolving Loratadine tablet at accelerated condition of 40^{o}C ± 2^{o}C/75% RH ± 5% (Initial)

Table 8.26: Stability results (Initial)

S. No.	Evaluation Parameter	Observation
		Formulation – F9
1	Physical Appearance	White,round, break-through, flat tablet.
2	Hardness (kg/cm^2)	3.0 ± 0.1
3	Disintegrate test (seconds)	12 ± 1.8973
4	Dissolution test (%)	99.10 ± 0.9422
5	Drug content (% w/w)	98.75 ± 0.01

8.4.2. Ageing studies for optimized formulation F9 of mouth dissolving Loratadinetablet at accelerated condition of 40°C ± 2°C/75% RH ± 5% (1st month)

Table 8.27: Stability results (1st month)

S. No.	Evaluation Parameter	Observation
		Formulation – F9
1	Physical Appearance	****
2	Hardness (kg/cm^2)	2.93 ± 0.577
3	Disintegrate test (seconds)	11.80 ± 1.632
4	Dissolution test (%)	99.02 ± 0.0115
5	Drug content (% w/w)	98.73 ± 0.17

**** = No Change

8.4.3. Ageing studies for optimized formulation F8 of mouth dissolving Loratadine tablet at accelerated condition of 40°C ± 2°C/75% RH ± 5%(2nd month).

Table 8.28: Stability results (2nd month)

S. No.	Evaluation Parameter	Observation
		Formulation – F9
1	Physical Appearance	****
2	Hardness (kg/cm^2)	2.93 ± 0.681
3	Disintegrate test (seconds)	11.65 ± 0.632
4	Dissolution test (%)	98.52 ± 0.0416
5	Drug content (% w/w)	98.70 ± 0.20

**** = No Change

8.4.4. Ageing studies for optimized formulation F8 of mouth dissolving Loratadinetablet at accelerated condition of 40°C ± 2°C/75% RH ± 5% (3rdmonth)

Table 8.29: Stability results (3rd month)

S. No.	Evaluation Parameter	Observation
		Formulation – F9
1	Physical Appearance	****
2	Hardness (kg/cm^2)	2.90 ± 0.516
3	Disintegrate test (seconds)	11.55 ± 1.471
4	Dissolution test (%)	98.70 ± 0.264
5	Drug content (% w/w)	98.64 ± 0.18

**** = No Change

8.4.5. Comparative Stability *In–Vitro* Release Study of optimized F9 formulation

Table 8.30: Comparative In-vitro dissolution data of formulation F9

Time in minute	Cumulative % Release of Loratadine (Mean ± S.D., n = 3)			
	Initial	First month	Second month	Third month
05	85.42 ± 1.673	85.10 ± 0.1	84.22 ± 0.230	83.99 ± 0.09
10	91.78 ± 0.905	90.68 ± 0.13	88.78 ± 0.1501	86.56 ± 0.103
15	96.40 ± 1.583	96.10 ± 0.1	94.56 ± 0.103	92.78 ± 0.04
30	99.10 ± 0.942	99.02 ± 0.011	98.52 ± 0.041	98.70 ± 0.264

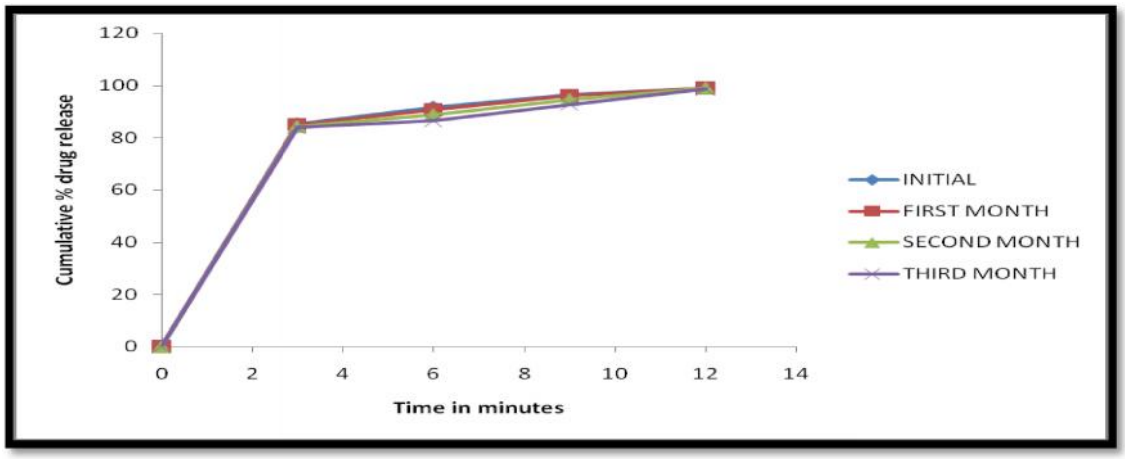


Figure 8.33: Comparative % Drug release of all three months with initial of optimized formulation F9.

8.4.6. Comparative Ageing studies for optimized formulation F9 with initial results

Table 8.31: Stability results (Initial to 3rd Month)

S. No.	Evaluation Parameter	Formulation- F9 observations			
		Initial	First month	Second month	Third month
1	Physical Appearance	White, round, Break - through, flat tablet.	No change	No change	No change
2	Hardness (kg/cm^2)	3.0±0.1	2.93±0.12	2.93±0.23	2.90 ± 0.1
3	Disintegrate test (seconds)	12±1.897	11.80±1.673	11.65±1.522	11.55±1.79
4	Dissolution test (%)	99.1± 0.9422	99.02±0.01	98.52±0.041	98.70±0.264
5	Drug content (% w/w)	98.75±0.01	98.73±1.123	98.70±0.114	98.64±0.136

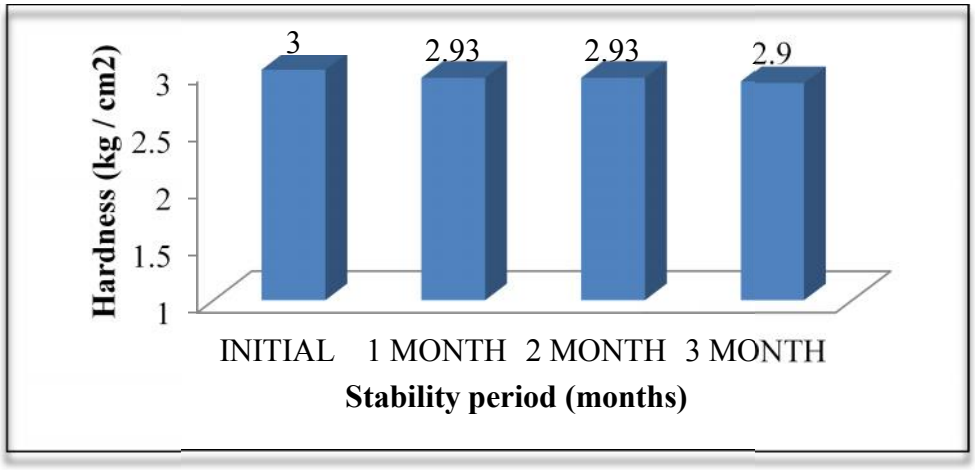


Figure 8.34: Comparison of Hardness for formulation F9 with initial and different stability period

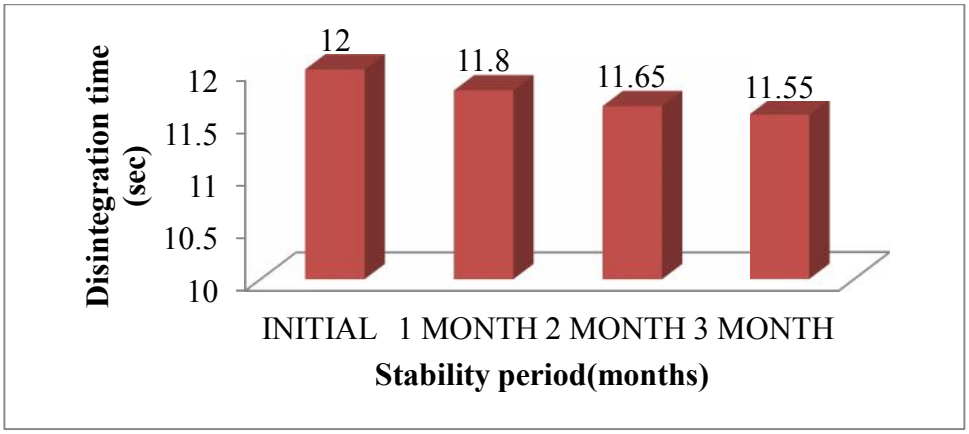


Figure 8.35: Comparison of Disintegrate time for formulation F9 with initial and different stability period

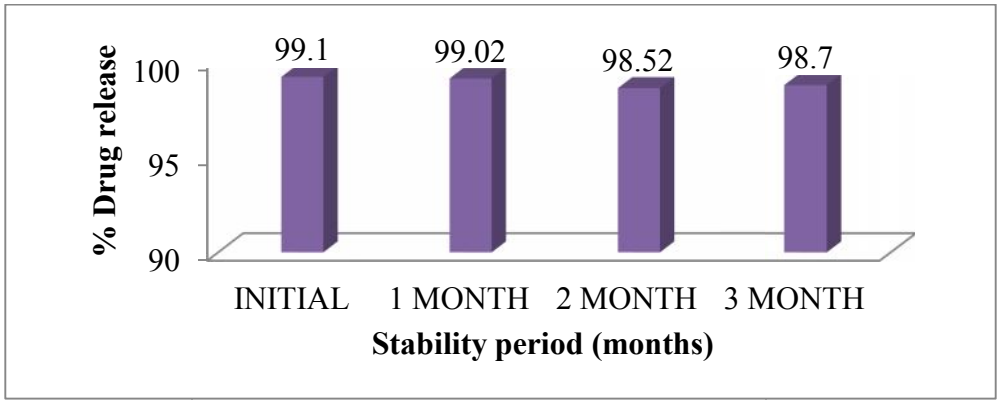


Figure 8.36: Comparison of Drug release for formulation F9 with initial and different stability period

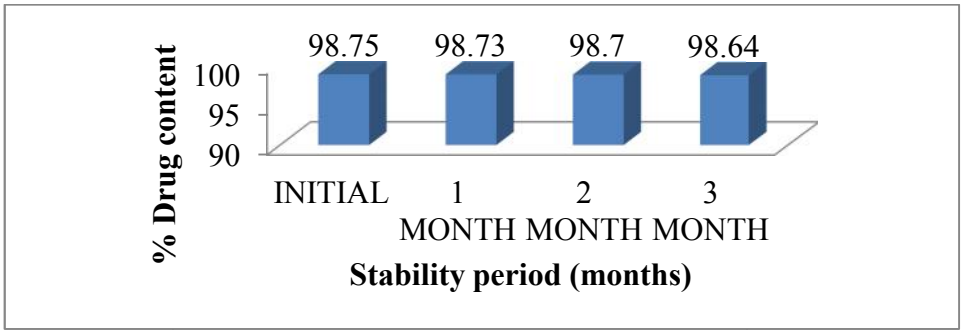


Figure 8.37: Comparison of Drug content for formulation F8 with initial and different stability period

Stability studies of formulation F9 were carried out by placing the samples at temperature 40^{o}C and different relative humidity conditions 75% RH. From the above observations it was found that there were no significant changes in disintegrate time, release characteristics and physicochemical properties of the tablets used in the release study. Based on the results it can be concluded that the formulated mouth dissolving tablets were stable at accelerated stability conditions (40^{o}C ± 2^{o}C and 75% ± 5% RH) over a period of 3 months. Even though its stability is assured for three months, further studies as per the ICH guidelines are to be needed to establish its shelf-life.

Summary and Conclusion

9. SUMMARY AND CONCLUSION

The present investigation was undertaken to fabricate and evaluate instant release mouth dissolving tablet of Loratadine with the main objective of quick onset of action followed by pleasant mouth feel and improved patient compliance.

Loratadine is act as an anti histaminic and used as potential drug to get the quick relief in suddenly arising allergic reactions like urticaria, angeoedema, in treatment of perennial and seasonal allergic rhinitis, considering this parameter there is a need formulate the Loratadine as fast disintegrating mouth dissolving tablet. Present Mouth dissolving tablet by passes the hepatic metabolism unlikely of the other conventional oral dosage forms which are relatively less bioavailable. This MDT gives absorption of drug from oral cavity, pharynx and oesophagus; results in quick onset of action, improved bioavailability and patient compliance.

The present study is an attempt to select best possible combination of superdisintegrants to formulate MDDDS of Loratadine which disintegrates within seconds in mouth, thereby reducing the time of onset of action, with maximum bioavailability of Loratadine.

Sodium starch glycollate, Crospovidone and Croscarmellose sodium were selected as super disintegrants. Microcrystalline cellulose is selected as diluents and it also act as a disintegrant in the lesser extent. Likewise the Mannitol used as diluents and it have the property to produce cooling sensation in the mouth. Aerosil added as a glident in all formulations in same concentrations. Magnesium sterate as a lubricant. Aspartame was

incorporated as sweetening and taste inhibiting agent. Whereas, strawberry used as flavoring agent, for to get the cool and pleasant mouth feel.

Drug-excipients interaction study was carried out using FT-IR i.e. by KBr pellet method (1:1). The FT-IR spectra revealed that there was no compatibility related problems between the drug and excipients used in the formulation.

Direct Compression method was used to formulate the tablets, because of its cost effectiveness, reduced number of manufacturing steps.

Pre-compression parameters; bulk density, tapped density,Compressibility index and Hausner's ratio for all formulations were found to be in good agreement of the prescribed limits. Showed good powder flow properties.

Post-compression parameters; hardness, friability, weight variation, drug content was evaluated and found to be acceptable with the prescribed limits.

Wetting time and swelling capacity of disintegrants are the important parameters for comparing efficiency of disintegrate process. The use ofhighest concentration of Crospovidone in F9 formulation showed highest hydration and swelling capacity of 11 seconds and 125.80 % respectively. Crospovidone has 5 to 10 folds more swelling capacity in just 10 seconds. Crospovidone showed faster disintegrate followed by Croscarmellose sodium and Sodium starch glycollate formulations.

Disintegrate time for all formulations was found in between 12 ± 1.67 to 30 ± 1.89 seconds. Disintegrate time was found to be very less for F9 formulation which contains highest concentration of Crospovidone.

Percent cumulative drug release for all nine formulations was found in the range of 88.94 ± 0.2214 to 99.10 ± 0.9422 %. Drug release was increased with the increased concentration of with crosspovidone. F9 formulation showed highest drug release i.e. 99.10% w/w in almost first 12 minutes.

In the present study, attempt was made to formulate instant palatable mouth dissolving tablets of Loratadine. From the studies carried out and above obtained results following conclusions are drawn;

Mouth dissolving tablet of Loratadine can be successfully prepared using selected different superdisintegrants, diluents and taste inhibiting agents by sensory approach using Direct Compression method.

Formulation F9 revealed promising results which was formulated by Crosspovidone in 5:4 ratio. This formulation exhibited highest water absorption and hydration capacity, showed least disintegrate time and highest percent drug release which provides quick onset of action and immediate relief in suddenly arising allergic reactions. Moreover, they showed pleasant mouth feel. This formulation satisfied all the tablet evaluation parameters for Mouth Dissolving Drug Delivery System. Hence, it was concluded that the F9 Formulation is optimized formulationamongst F1 to F9.

Optimized Formulation F9 was tested for Accelerated stability as per ICH guidelines was found to be a stable at $40^{o}C \pm 2^{o}C$ temperature and 75% ± 5% relative humidity for three months.

Undoubtedly Loratadine MDT will surely give the rapid onset of action, quick relief, low side effects, pleasant mouth feel, good stability, improved patient compliance, and its popularity in the near future.

Future Prospectus

10. SCOPE FOR FURTHER STUDY

SCOPE FOR FURTHER STUDY

In the present work the mouth dissolving tablets Loratadine were prepared by using different superdisintegrants as Croscarmellose sodium, Sodium starch glycollate and Crospovidone by direct compression method. In this work only physiochemical characterization, formulation and *in-vitro* evaluation of Mouth dissolving tablets Loratadine was performed. Along with *in-vitro* studies *in-vivo* studies of drug is most important. In future *in-vivo* studies are required to set the *in-vitro in-vivo* correlation which is necessary for development of successful formulation and also long term stability studies are necessary.

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